Protocol I2V-MC-CXAD (b)

Protocol I2V-MC-CXAD (b) A Phase 1a/1b Study of CXCR4 Peptide Antagonist (LY2510924) Administered in Combination with the Anti-PD-L1 Antibody, Durvalumab (MEDI4736), in Advanced Refractory Solid Tumors

NCT02737072

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1. Protocol I2V-MC-CXAD(b)
A Phase 1a/1b Study of CXCR4 Peptide Antagonist (LY2510924) Administered in Combination with the Anti-PD-L1 Antibody, Durvalumab (MEDI4736), in Advanced Refractory Solid Tumors

LY2510924 and Durvalumab (MEDI4736)

This is a multicenter, nonrandomized, open-label, dose-escalation Phase 1a study of LY2510924 combined with durvalumab (MEDI4736) in patients with advanced refractory solid tumors followed by an open-label, 2-expansion-arms, Phase 1b study in patients with advanced refractory pancreatic and ovarian cancer.

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Protocol Electronically Signed and Approved by Lilly on: 22 February 2016
Amendment (a) Electronically Signed and Approved by Lilly: 21 July 2016
Amendment (b) Electronically Signed and Approved by Lilly
on approval date provided below.

Approval Date: 12-Oct-2016 GMT

2. Synopsis

The chemokine (C-X-C Motif) receptor 4 (CXCR4) and its only known ligand, α-chemokine stromal cell-derived factor-1 (SDF-1) are believed to play an important role in the regulation of organ-specific metastasis, as well as tumor growth, invasion, survival, and angiogenesis. CXCR4 is functionally expressed or overexpressed in a variety of solid tumor cancers, lymphoma, and chronic lymphocytic leukemia (Balkwill 2004; Peng et al. 2015). Within hypoxic areas of tumors, both SDF-1 secretion by fibroblasts and CXCR4 expression on tumor cells increase, which stimulate tumor cell growth, migration, and invasion. SDF-1 promotes tumor growth in a paracrine fashion by directly stimulating tumor cell proliferation and survival via CXCR4. Recently, CXCR4 was demonstrated to play a role in cancer immunotherapy via T-cell mobilization and redistribution in the tumor microenvironment (Righi et al. 2011; Feig et al. 2013; Gil et al. 2014).

Durvalumab (MEDI4736) is in development as a potential anticancer therapy for patients with advanced solid tumors and hematological malignancies. Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death–ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Partial efficacy data are available for the ongoing Phase 1/2 Study CD-ON-MEDI4736-1108 in patients with solid tumors (of whom, 456 were response evaluable). Across the PD-L1-positive tumors (n=383 of 456 patients), overall response rate (ORR) was highest (>10%) for bladder cancer (33.3%; 1 of 3 response evaluable patients), advanced cutaneous melanoma (33.3%; 1 of 3 response evaluable patients), hepatocellular carcinoma (HCC) (33.3%; 1 of 3 response evaluable patients), non–small-cell lung cancer (NSCLC) (26.7%; 23 of 86 response evaluable patients), and squamous cell carcinoma of the head and neck (SCCHN) (18.2%; 4 of 22 response evaluable patients). Further, in the PD-L1-positive subset, disease control rate (DCR)-24w was highest (>10%) in advanced cutaneous melanoma (66.7%), NSCLC (36.0%), HCC (33.3%), bladder cancer (33.3%), and SCCHN (18.2%). While the ORR in these tumor types are appreciable, other indications have either low to no efficacy with PD-L1 treatment alone, possibly due to lack of immune cell infiltration in the tumor microenvironment.

The combination of CXCR4 inhibitor with anti-PD-L1 immunotherapy has shown increased infiltration of T cells into tumors and tumor regression in an in vivo pancreatic cancer mouse model (Feig et al. 2013). This study will investigate the effects of CXCR4 inhibition (LY2510924) in combination with PD-L1 inhibition (durvalumab).

This study is a Phase 1a/1b open-label study that will be conducted in 2 parts. The Phase 1a portion of this study will consist of a dose assessment of the safety and tolerability of LY2510924 administered at 20, 30, or 40 mg subcutaneously (SQ) daily in combination with durvalumab 1500 mg intravenously (IV) once every 28 days in patients with advanced refractory solid tumors. The LY2510924 dose in the Phase 1b portion of this study will be based on Phase 1a results. The Phase 1b portion will include expansion arms in 2 indications, pancreatic and ovarian cancer (N=15 each arm). Enrollment will be complete when the expansion arms

have reached the prespecified enrollment target. Safety and efficacy analysis of each expansion arm will be performed independently of the other arm.

Clinical Protocol Synopsis: Study I2V-MC-CXAD

Name of Investigational Product: LY2510924 and durvalumab (MEDI4736)	
Title of Study: A Phase 1a/1b Study of CXCR4 Peptide Antagonist (LY2510924) Administered in Combination with the Anti-PD-L1 Antibody, Durvalumab (MEDI4736), in Advanced Refractory Solid Tumors	
Number of Planned Patients: Phase 1a: approximately 12-15 patients Phase 1b: approximately 30 patients	**Phase of Development:** 1a/1b
Length of Study: Approximately 2 years Planned first patient visit: August 2016 Planned last patient visit: August 2018	
Objectives: **Primary objective for the dose escalation:** To assess the safety and tolerability of LY2510924 SQ daily in combination with durvalumab by identifying dose-limiting toxicities (DLTs) and the maximum-tolerated dose (MTD) of the combination in patients with advanced (metastatic and/or unresectable) solid tumors. **Primary objective for the dose expansion:** To assess the safety of LY2510924 SQ daily in combination with durvalumab in patients with advanced pancreatic and ovarian cancers. **Secondary objectives:** • To characterize the pharmacokinetics (PK) of LY2510924 and durvalumab when co-administered • To characterize the immunogenicity of durvalumab when administered in combination with LY2510924 • To assess the antitumor activity of the combination of LY2510924 and durvalumab in patients with advanced solid tumors **Exploratory objectives:** • To examine biomarkers, including pharmacodynamic markers, relevant to LY2510924 and durvalumab, including but not limited to, immune cells/immune functioning, drug targets, cancer-related pathways and the disease state, and to correlate these markers with clinical outcome	
Study Design: This is a Phase 1a/1b open-label study that will be conducted in 2 parts. The first part (Phase 1a) of the study will consist of a dose-escalation assessment of the safety and tolerability of LY2510924 administered with durvalumab in patients with advanced refractory solid tumors. The second part (Phase 1b) of the study will include 2 expansion arms in advanced pancreatic cancer (N=approximately 15 patients) and ovarian cancer (N=approximately15 patients), all receiving LY2510924 (dose determined from Phase 1a) with durvalumab.	

Diagnosis and Main Entry Criteria:

Inclusion:

- Phase 1a: Have a histologic or cytological confirmed advanced solid tumor (see American Joint Committee on Cancer Staging Criteria; Edge et al. 2009) and must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed to provide clinical benefit for their disease or the patient has refused available standard therapies.
- Phase 1b: Histologic or cytologic confirmation of advanced cancer in the following tumor types:
  - Pancreatic cancer
    - Cytologically or histologically confirmed pancreatic adenocarcinoma (excluding other pancreatic malignancies [eg, acinar cell carcinomas, adenosquamous carcinomas, and neuroendocrine islet cell neoplasms])
    - Metastatic disease or locally advanced, unresectable disease
    - Have had disease progression, be refractory or intolerant to no more than 2 prior systemic regimens for locally advanced or metastatic pancreatic cancer. Patients who have received prior neoadjuvant therapy and who now have metastatic disease, must receive FOLFIRINOX, FOLFOX, single-agent gemcitabine, gemcitabine/nab-paclitaxel, or TS-1 (tegafur gimeracil oteracil potassium) prior to enrollment on this study.
  - Ovarian cancer
    - Cytologically or histologically proven epithelial ovarian cancer (except borderline ovarian tumor histology), fallopian tube cancer, or primary peritoneal cancer with evidence of recurrence or refractory disease, which is advanced and not amenable to curative surgery or radiotherapy (International Federation of Gynecology and Obstetrics Staging; Odicino et al. 2008).
    - Have recurrence of cancer at least 6 months after completion of first-line platinum-based therapy.
    - Have received chemotherapy for recurrence of disease, but not exceeding 4 lines of therapy during which time disease may be platinum sensitive or resistant.
- Have provided tissue from a newly obtained core or excisional biopsy of a tumor lesion or a recent biopsy defined by ≤3 years since last documented progression of disease. (Note: patients for whom newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived specimen can be submitted upon agreement from sponsor and if not restricted by local regulations)
  - For ovarian expansion arm only: Be able to provide tissue (newly obtained core or excisional biopsy of tumor lesion) from an on-treatment biopsy for biomarker analysis.
- Have at least 1 measurable lesion assessable using standard techniques by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al. 2009).

Exclusion:

- Active autoimmune disorders, or prior documented severe autoimmune or inflammatory disorders requiring immunosuppressive treatment (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of diverticulosis, irritable bowel syndrome, or other serious gastrointestinal chronic conditions associated with diarrhea); systemic lupus erythematosus; Wegener Granulomatosis (with polyangiitis), Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion: vitiligo or alopecia, diabetes mellitus type I or resolved childhood asthma/atopy; hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement; psoriasis not requiring systemic treatment; any chronic skin condition that does not require systemic therapy; or celiac disease controlled by diet alone. Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
- Require escalating or chronic supraphysiologic doses of corticosteroids (>10 mg/day of prednisone or an equivalent corticosteroid) for control of their disease or immunosuppressive agents (eg, cyclosporine) for any reason.
- Have had prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated

antigen-4 antibody (including but not limited to ipilimumab, durvalumab or tremelimumab) or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3.

Test Product, Dosage, and Mode of Administration: A cycle is 28 days in duration.
LY2510924 at 20 mg, 30 mg, or 40 mg self-administered SQ once daily in Phase 1a; LY2510924 will be self-administered in a similar fashion in Phase 1b at the selected Phase 1a dose.
Durvalumab: IV administration of durvalumab 1500 mg on Day 1 of each cycle for Phase 1a and Phase 1b.

Planned Duration of Treatment: Patients will receive study therapy until the patient fulfills 1 of the criteria for study discontinuation. Patients may continue on combination therapy beyond initial radiological disease progression in the absence of clinically significant deterioration. If a patient experiences an adverse event (AE) that requires the patient be discontinued from durvalumab or LY2510924, the patient should be discontinued from both study drugs.

Criteria for Evaluation:
Safety: Hematology, clinical chemistry, urinalysis, vital sign collection, weight, electrocardiograms (ECGs), echocardiography (screening for all patients; subsequently if clinically indicated), physical examinations, concomitant medication collection, dose adjustments, AE/DLT/serious adverse events (SAE) collection using International Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.
Efficacy: Eastern Cooperative Oncology Group (ECOG) performance status, tumor assessment via RECIST v 1.1.
Biomarkers/Pharmacodynamic: Blood collection, tumor biopsies.
Pharmacokinetic: Concentrations of LY2510924 and durvalumab in plasma or serum will be assayed using validated methods.
Immunogenicity: Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies (ADAs) in the presence of durvalumab.

Statistical Methods:
Statistical: Up to approximately 45 patients may be enrolled in this study. The Bayesian model-based, toxicity-band method will be followed to assist dose escalation during Phase 1a. The sample size for Phase 1a will primarily be limited by the incidence of DLTs. The anticipated sample size for Phase 1a ranges from approximately 12 to 15 patients. The sample size of approximately 15 patients per tumor type in Phase 1b has been selected to allow adequate assessment of safety at the recommended dose level. The first tumor evaluation will occur at 2 months.
Safety: All patients who receive at least 1 dose of either study drug will be evaluated for safety. Summaries and listings for all safety data collected will be provided.
Efficacy: Tumor response data will be summarized by the best overall response, overall response rate and disease control rate. Time-to-event variables such as progression-free survival, time to response, duration of response and overall survival will also be summarized and the Kaplan-Meier method will be used to estimate the survival curves, medians, and survival rates as applicable.
Biomarkers/Pharmacodynamic: Exploratory biomarkers will be summarized and assessed for correlations with clinical outcomes. Biomarker relationships by tumor type, changes in biomarker levels at baseline and over time, and differences among dose levels or exposure will be explored as possible.
The pharmacodynamic effect from all patients undergoing pharmacodynamic assessments will be explored.
Pharmacokinetic: Summary statistics will be tabulated for the PK parameters of LY2510924 and durvalumab by dose and study day.
Immunogenicity: Immunogenicity incidence will be summarized, and correlation to durvalumab, 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 infusion-related reactions (IRR).

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4. Abbreviations and Definitions

Term	Definition
ADA	antidrug 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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC	area under the plasma drug concentration-time curve
AUC_{SS}	AUC at steady state
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).
blinding/masking	a procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. Single-blinding usually refers to the patient(s) being unaware, and double-blinding usually refers to the patient(s), investigator(s), monitor(s), and in some cases select sponsor personnel, being unaware of the treatment assignment(s).
CD	cluster of differentiation
CE	carboplatin/etoposide
CI	confidence interval
CL/F (or CL)	apparent systemic clearance
C_{max}	maximum observed concentration

$C_{max,ss}$	C_{max} at steady state
collaborator	For this study, collaborator is defined as AstraZeneca (London, United Kingdom).
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.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CR	complete response
CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRM	continual reassessment method
CRP	clinical research physician
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	chemokine (C-X-C Motif) receptor 4
DCR	disease control rate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
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/IRB	ethical review board/institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
GCP	good clinical practice
GTP	guanosine-5'-triphosphate
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
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.
interim analysis	an analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.
intravenous	IV
investigational product (IP)	a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. Investigational product includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form 2. used for an unauthorized indication or 3. used to gain further information about the authorized form
investigator	a person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRR	infusion-related reaction
irRC	immune-related response criteria
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.

LV	left ventricular
LVEF	left ventricular ejection fraction
mAb	human monoclonal antibody
monitor	a person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to patients, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
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
patient	a subject with a defined disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PK	pharmacokinetic
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rescreen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event

SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
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. In this study, screening involves diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	a patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SDF-1	stromal cell-derived factor-1
sPD-L1	soluble programmed cell death ligand 1
sponsor	the party who takes responsibility for the initiation, management and/or financing of a clinical study.
SQ	subcutaneous
study completion	This study will be considered complete after the final analysis (to occur no more than 12 months after last patient enters treatment) and evaluation of the primary objective and secondary objectives have been performed.
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TPO	third-party organization
ULN	upper limit of normal
v	version
WT	body weight

5. Introduction

5.1. Cancer Immunotherapy

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death–ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency. In a number of these cancers, including lung (Mu et al. 2011), renal (Thompson et al. 2005; Thompson et al. 2006; Krambeck et al. 2007), pancreatic (Nomi et al. 2007; Loos et al. 2008; Wang et al. 2010), ovarian cancer (Hamanishi et al. 2007), and hematologic malignancies (Andorsky et al. 2011; Brusa et al. 2013) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

5.1.1. Immune Checkpoint Inhibitors Targeting PD-1/PD-L1

The programmed cell death 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. ***Immune checkpoints, such as PD-1 and PD-L1, have been targeted with antagonist mAbs, such as PD-1 antibodies nivolumab and pembrolizumab and PD-L1 antibody durvalumab (MEDI4736).***

5.1.2. Rationale for Combination Therapy and Selection of Expansion Tumor Types

PD-1 inhibitors provide the opportunity to restore T-cell immunity via blocking both its inhibitory interactions with PD-L1 and PD-L2. In settings of chronic stimulation, as in cancer, PD-L1 signals through T-cell PD-1 to "turn off" T cells in order to minimize damage to healthy tissue. Blocking PD-1/PD-L1 allows T cells to maintain their effector function. However, in an immunocompetent pancreatic mouse tumor model single-agent anti-PD-L1 did not induce tumor regression due to lack of immune cells; CXCR4 blockade ensures adequate T cells are present in the tumor microenvironment (Feig et al. 2013). Thus blockade of both chemokine (C-X-C Motif) receptor 4 (CXCR4) and PD-L1 has the potential to reverse the immune escape associated with these molecules in cancer and to potentially provide immune restoration to improve tumor control. The combination of CXCR4 and PD-1/PD-L1 inhibition is hypothesized to provide antitumor activity because CXCR4 inhibition may promote T-cell accumulation and synergize with anti-PD-L1, thereby inducing cancer regression through T-cell regulation.

The combination may be potentially effective in several tumor types, including pancreatic and ovarian cancers. A preclinical autochthonous model of pancreatic ductal adenocarcinoma demonstrated that the addition of a CXCR4 inhibitor (AMD3100) resulted in the inhibition of α-chemokine stromal cell–derived factor-1 (SDF-1; also known as CXCL12), the ligand to CXCR4 receptor, promotion of T-cell accumulation in the tumor and synergism with

anti-PD-L1, inducing cancer regression through T-cell regulation (Feig et al. 2013). These studies along with increased expression of CXCR4 in pancreatic cancer (Marchesi et al. 2004) support this tumor type as an indication for the combination of LY2510924 and durvalumab. Similarly, ovarian cancer also has been shown to have increased expression of CXCR4 (Scotton et al. 2002). High CXCR4 expression has been associated with poor prognosis in ovarian cancer (Liu et al. 2014). In an immunocompetent mouse model of epithelial ovarian cancer, treatment of tumors with selective CXCR4 antagonist, AMD3100, resulted in selective reduction of intratumoral FoxP3+ regulatory T cells, which are involved in the inhibition of tumor infiltrating lymphocytes (Righi et al. 2011). Therefore, these studies warrant further investigation of ovarian cancer as another indication for the combination of LY2510924 and durvalumab.

This study is a Phase 1a/1b open-label study that will be conducted in 2 parts. The Phase 1a portion of this study will consist of a dose assessment of the safety and tolerability of LY2510924 administered at 20, 30, or 40 mg subcutaneously (SQ) daily in combination with durvalumab 1500 mg intravenously (IV) once every 28 days in patients with advanced refractory solid tumors. The LY2510924 dose in the Phase 1b portion of this study will be based on the Phase 1a results. The Phase 1b portion will include expansion arms in 2 indications, pancreatic and ovarian cancer (N=approximately 15 patients in each arm). Enrollment will be complete when the expansion arms have reached the prespecified enrollment target. Safety and efficacy analysis of each expansion arm will be performed independently of the other arm.

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.

5.2. Rationale for Protocol Amendment (a)

The I2V-MC-CXAD protocol was amended to make the following changes:

- include FOLFOX as an accepted prior therapy for pancreatic cancer
- allow for enrollment of patients with celiac disease if their disease is controlled only with diet
- add echocardiography at baseline to document initial left ventricular (LV) function. Additionally, echocardiography may be performed on-study as clinically indicated to determine left ventricular ejection fraction (LVEF)/LV dysfunction and any change in cardiac size or function. An echocardiography guidance was included as a protocol attachment (Attachment 12).
- exclude patients with history of QT interval prolongation, history of uncontrolled cardiac arrhythmias or congenital long QT syndrome, or who require drugs known to cause QT prolongation
- change the exclusion criterion for mean QTc interval from ≥470 ms to ≥450 ms to align with ICH E14 guidelines
- observe the initial patient in the 40-mg cohort in Phase 1a for 2 weeks, after which additional patients will be enrolled after notification from the sponsor. This allows for a

safety assessment prior to enrolling subsequent patients since this dose level has not previously been investigated.
- clarify that final analysis will be conducted no more than 12 months after the last patient enters treatment
- allow dose interruption up to 12 weeks. Management of immune-mediated adverse events (AEs), including steroid tapering, allows a 12-week window for resolution before discontinuing study treatment.
- add dose-limiting toxicity (DLT) and LY2510924 discontinuation criteria of ≥Grade 3 QT prolongation AE per Common Terminology Criteria for Adverse Events (CTCAE) criteria
- clarify an exclusion to the DLT list. Grade 3 thrombocytopenia not associated with bleeding that requires clinically significant medical intervention and improves by at least 1 grade within 3 days is not considered a DLT.
- clarify LY2510924 dose adjustments, delays, and discontinuations and revise a discontinuation criterion from LY2510924 treatment. Patients with combined elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) AND total bilirubin values meeting discontinuation parameters as described in the DLT definition should be considered for permanent discontinuation based on clinical judgment.
- include scheduled electrocardiogram (ECG) assessments to assess QT interval length periodically during study therapy
- make minor clarifications and changes.

5.3. Rationale for Protocol Amendment (b)

The I2V-MC-CXAD protocol (a) was amended to make the following changes:

- Section 5.5.2.4: Clinical safety information on durvalumab updated.
- Section 6.1.3: Exclusion Criterion [16] expanded to include previous participation in any randomized controlled trial that included arms with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3, rather than only either durvalumab or tremelimumab.
- Synopsis and Section 6.2: Clarified that patients will be allowed to continue until they fulfill 1 or more of the study discontinuation criteria.
- Sections 6.2 and 8.3.1.2: Clarified that patients will not be permitted to continue study therapy if progression occurs after confirmed response.
- Section 7.2.2.1: Added or modified existing DLT criteria to:
    - ≥Grade 3 leukocytosis (leukocytes >100,000/μL) of any duration, or leukocytosis/granulocytosis causing clinical symptoms
    - Any Grade 4 non-laboratory AE
    - Any Grade 3 laboratory value, and modified stipulations that the abnormal value must be associated with clinically significant symptoms and persist for >7 days
    - Any Grade 4 laboratory abnormalities

- Section 7.2.2.2: For Phase 1a, any DLT-equivalent toxicities observed in Cycle 2 and beyond will also be considered in dose escalation and determining MTD/recommended Phase 2 dose. Additionally, if the DLT observation period is extended to Cycle 2, patients discontinuing Cycle 2 in the absence of DLT-equivalent toxicity will be evaluable for DLT assessments.
- Section 7.2.4: Wording added that for Phase 1a and 1b, the DLT observation period will be extended to Cycle 2 if a DLT-equivalent toxicity is observed during Cycle 2 in any cohort in Phase 1a.
- Table CXAD.7.2: Dose adjustment of LY2510924 to align with newly added DLT criterion for leukocytosis.
- Section 8.1.3.1: Typographical error was corrected.
- Section 8.3.1.2: Patients with a decline in Eastern Cooperative Oncology Group (ECOG) performance status >1 will not be permitted to continue study treatment after confirmed progression of disease.
- Section 10.10: Wording added that if the DLT-observation period is extended to 2 cycles during Phase 1a, analysis will include DLT-equivalent toxicities occurring in Cycle 2.
- Attachment 1 and Attachment 4 Correction: For serum, plasma, and whole blood samples for biomarkers, baseline whole blood samples must be collected ≤7 days prior to Cycle 1 Day 1.
- Attachment 4 Correction: immunogenicity samples will be collected 90 days post durvalumab treatment.
- Attachment 11: Durvalumab dose modification guidelines have been updated.

Attachment 13 contains a detailed list of changes made in this amendment. Some minor editorial changes may not be listed.

5.4. Objectives

5.4.1. Primary Objective

Dose Escalation

The primary objective of the dose-escalation part of this study is to assess the safety and tolerability of LY2510924 SQ daily in combination with durvalumab by identifying DLTs and the maximum-tolerated dose (MTD) of the combination in patients with advanced (metastatic and/or unresectable) solid tumors.

Dose Expansion

The primary objective of the dose-expansion part of this study is to assess the safety of LY2510924 SQ daily in combination with durvalumab in patients with advanced pancreatic and ovarian cancers.

5.4.2. Secondary Objectives

The secondary objectives of this study are:

- To characterize the pharmacokinetics (PK) of LY2510924 and durvalumab when co-administered
- To characterize the immunogenicity of durvalumab when administered in combination with LY2510924
- To assess the antitumor activity of the combination of LY2510924 and durvalumab in patients with advanced solid tumors

5.4.3. Exploratory Objectives

The exploratory objective of this study is to examine biomarkers, including pharmacodynamic markers, relevant to LY2510924 and durvalumab, including but not limited to, immune cells/immune functioning, drug targets, cancer-related pathways and the disease state, and to correlate these markers with clinical outcome.

5.5. General Introduction to LY2510924 and Durvalumab

5.5.1. LY2510924

5.5.1.1. LY2510924 Chemokines, SDF-1, and CXCR4

Chemokines are important molecules that guide the migration of cells from one tissue to another. The CXCR4 is a transmembrane G-protein–coupled receptor. CXCR4 and its only known ligand, α-chemokine stromal-cell derived factor-1 (SDF-1) are believed to play an important role in the regulation of organ-specific metastasis, as well as tumor growth, invasion, survival, and angiogenesis (Balkwill 2004; Peng et al. 2015). The CXCR4/SDF-1 axis is involved in the migration of hematopoietic stem cells and lymphocytes, and both are required for normal murine fetal development (Balkwill 2004). SDF-1 is expressed widely throughout the body, and SDF-1 concentrations in the tissue play an important role in signaling whether CXCR4+ cells should stay in their present environment or migrate to other tissues. For instance, if local SDF-1 concentrations increase in response to a stimulus, CXCR4+ cells may follow the gradient to the SDF-1-rich environment. Similarly, static concentrations of SDF-1 will prevent the migration of CXCR4+ cells from the tissue; however, blocking the interaction of SDF-1 with CXCR4 results in rapid mobilization of stem cells and leukocytes into the peripheral blood.

CXCR4 is functionally expressed or overexpressed in a variety of solid tumor cancers, lymphoma, and chronic lymphocytic leukemia (Balkwill 2004; Peng et al. 2005). Within hypoxic areas of tumors, both SDF-1 secretion by fibroblasts and CXCR4 expression on tumor cells increase, which stimulate tumor cell growth, migration, and invasion. SDF-1 promotes tumor growth in a paracrine fashion by directly stimulating tumor cell proliferation and survival via CXCR4. Stromal cells in tissues such as bone, liver, and lungs secrete SDF-1, creating a concentration gradient that induces directional migration of CXCR4 expressing cancer cells toward these tissues (Kucia et al. 2005). Recently, CXCR4 was demonstrated to play a role in

cancer immunotherapy via T-cell mobilization and redistribution in the tumor microenvironment (Righi et al. 2011; Feig et al. 2013; Gil et al. 2014).

More information about the known and expected benefits, risks and reasonably anticipated AEs may be found in the Investigator's Brochure (IB). Information on serious adverse events (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 also be found in the IB.

5.5.1.2. CXCR4 Peptide Antagonist LY2510924 and Its Mechanism of Action

LY2510924 is a potent and selective peptide antagonist of CXCR4 in vitro and in vivo and inhibits SDF-1 binding to CXCR4 in human, monkey, mouse, and rat cells. LY2510924 inhibited SDF-1α binding to human CXCR4 in a dose-dependent manner in 2 different tumor cell lines (leukemia and lymphoma) with an IC_{50} of 0.0797 to 0.3016 nM (Peng et al. 2015).

LY2510924 is specific for CXCR4, blocks binding of SDF-1α to CXCR4, and does not demonstrate agonist activity. In an in vitro ligand-binding assay, LY2510924 did not bind to CCR1, CCR2, CXCR2 and CXCR3, serotonin, dopamine, or specific opioid receptors; however, in a cell surface receptor mini-panel, LY2510924 significantly inhibited Alpha 2 adrenergic, Ghrelin, muscarinic, NK2, and opioid (nonspecific) receptors at 10 μM. LY2510924 inhibited SDF-1 binding to CXCR4 of monkey, mouse, and rat in a dose-dependent manner with IC_{50} of 0.097, 2.832, and 2.218 nM, respectively. In vitro, SDF-1α induces guanosine-5'-triphosphate (GTP) binding and initiates a signaling cascade that results in chemotaxis in a dose-dependent manner; however, under identical conditions, LY2510924 interaction with CXCR4 does not cause GTP binding or chemotaxis, confirming that LY2510924 has no apparent agonist activity.

5.5.1.3. Summary of Clinical Experience

I2V-MC-CXAA (CXAA) study was a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study of SQ LY2510924 in patients with advanced or metastatic cancer for whom no treatment of higher priority existed. Study CXAA consisted of a dose-escalation phase, followed by a dose-confirmation phase. Elevated CD34+ counts were seen in patients treated in CXAA study in a dose-dependent manner. The PK/pharmacodynamic modelling based on CD34+ cells from CXAA study indicated a plateau in the increase of CD34+ in peripheral blood for the dose levels above 20 mg but this was based on dose levels up to 30 mg only (n=7 patients treated at this dose on CXAA study, refer to Section 5.6 for further details). There were 9 SAEs experienced by 7 subjects (study disease [3 subjects]; and abdominal abscess, cerebellar tumor, dyspnea, chest pain, pulmonary embolism, and respiratory arrest [each 1 subject]); none of the SAEs were related to study drug. Six subjects (13.3%) died within 30 days of their last dose of study drug; none of the deaths were related to study drug. Five subjects (2 subjects from each the 2.5 and 20 mg/day dose cohort and 1 subject from the 1.0 mg/day cohort) died due to study disease; 1 subject (10 mg/day dose cohort) died due to an SAE (respiratory arrest).

Two Phase 2 combination studies have been completed; studies in renal cell carcinoma (RCC, 12V-MC-CXAB [CXAB]) and small cell lung cancer (SCLC, 12V-MC-CXAC [CXAC]) in which 119 patients received LY2510924 in combination with the standard of care at a dose of 20 mg daily SQ. In Study CXAB (RCC), LY2510924 was administered with sunitinib

(72 patients) versus sunitinib alone (36 patients). The most frequent treatment-emergent adverse events (TEAEs) reported in the LY2510924 + sunitinib arm versus sunitinib-alone arm were fatigue (69.4% vs 55.6%), nausea (48.6% vs 50%), diarrhea (38.9% vs 52.8%), anemia (34.7% vs 16.7%), dysgeusia (31.9% vs 30.6%), thrombocytopenia (27.8% vs 22.2%), rash (26.4% vs 11.1%, vomiting (25% vs 22.2%), dizziness (23.6% vs 19.4%), mucosal inflammation (23.6% vs 27.8%), decreased appetite (23.6% versus 22.2%) and hypertension (22.2% versus 33.3%). All deaths on study were due to disease progression except for 1 patient in the LY2510924 and sunitinib arm who died due to an event unrelated to drug therapy. In Study CXAC (SCLC), LY2510924 was combined with carboplatin/etoposide (CE) (47 patients) versus CE only (43 patients). The most common treatment-emergent AEs that occurred more frequently (>5%) in the LY2510924+CE arm than in the CE arm were anemia (62% vs 49%), vomiting (32% vs 23%), leukopenia (28% vs 9%), back pain (19% vs 7%), injection site pain (19% vs 0%), exertional dyspnea (15% vs 2%), and dysgeusia (12% vs 2%). No patients in this study died during treatment due to AEs. Both studies indicate that LY2510924 is able to be safely administered at this dose. However, neither study demonstrated sufficient efficacy of LY2510924 when given with standard of care for advanced RCC or SCLC.

5.5.1.4. Biomarkers

CXCR4 and SDF-1 interaction is critical for the retention of CD34+ stem cells and immune cells in bone marrow. In preclinical models, treatment with LY2510924 showed significant pharmacodynamics effects by increasing CD34+ stem cells and white blood cells (including neutrophils and lymphocytes) in the circulation. These pharmacodynamic effects were also observed in humans in a Phase 1 clinical study (Galsky et al. 2014). Therefore, CD34+ stem cells and total white blood cells including neutrophils and lymphocytes can be used as exploratory pharmacodynamic biomarkers in this study.

Additionally, the infiltration and distribution of T cells, and their relationship with tumor cells and stromal cells in the tumor microenvironment can be further explored as biomarkers.

5.5.2. Durvalumab

5.5.2.1. Programmed Cell Death–Ligand 1 (PD-L1)

Programmed cell death–ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir et al. 2008; Park et al. 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen, 2008).

5.5.2.2. Background on Durvalumab

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death–ligand 1 (PD-L1 (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to PD-1 (CD279) and CD80 (B7-1). 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 immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

5.5.2.3. Summary of Nonclinical Experience

The nonclinical experience is fully described in the current version of the durvalumab IB.

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays.

5.5.2.4. Summary of Clinical Experience

Clinical experience with durvalumab is fully described in the current version of the durvalumab IB.

As of 12 July 2015, a total of 1883 patients have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1883 patients, 1279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

Pharmacokinetics and Product Metabolism

Study CD-ON-MEDI4736-1108: As of 09 Feb 2015, PK data were available for 378 patients in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve (AUC) from 0 to 14 days increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated apparent systemic clearance (CL) at doses <3 mg/kg and approaches linearity at doses ≥3 mg/kg. Near complete target saturation (soluble programmed cell death–ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition,

PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, >90% of patients are expected to maintain PK exposure ≥40 μg/mL throughout the dosing interval.

As of 09 February 2015, a total of 388 patients provided samples for antidrug antibody (ADA) analysis. Only 8 of 388 patients (1 patient each in 0.1-, 1-, 3-, and 15-mg/kg cohorts, and 4 patients in 10-mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 patient in the 3-mg/kg cohort.

Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. Potential risks are events with a potential inflammatory mechanism which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. These risks include gastrointestinal AEs such as colitis and diarrhea, pneumonitis, nephritis and acute renal failure; hepatic AEs such as hepatitis and liver enzyme elevations, and dermatitis; and endocrinopathies such as hypo- and hyper-thyroidism, hypophysitis, and adrenal insufficiency. Additional treatment-emergent immune-related events, including pancreatitis, neuropathy, and neuromuscular toxicity, have been reported with checkpoint inhibitor treatment. These events are manageable by available/established treatment guidelines as described in the study protocol.

Adverse Event Profile of Durvalumab Monotherapy

Identified risks with durvalumab are diarrhea, increases in transaminases, pneumonitis, and colitis.

Potential risks include endocrinopathies (hypo- and hyper-thyroidism, hypophysitis, and adrenal insufficiency), hepatitis/hepatotoxicity, neurotoxicities, nephritis, pancreatitis, dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, and immune complex disease. Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies, AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 3.5% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established

treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines in Attachment 11).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

5.6. Rationale for Selection of Dose

LY2510924

A dose range of 20, 30, and 40 mg of LY2510924 administered SQ daily was selected based on the overall clinical information from the 3 studies completed. In the first-in-human dose CXAA study, a predefined DLT criterion was used for the elevation of absolute neutrophil account (ANC >25 000) and 2 of 7 patients exceeded this level at the 30 mg dose during treatment. This led to the MTD dose of 20 mg. However, it is notable that high levels of ANC were not reported as clinically significant. In addition, the 2 Phase 2 studies, CXAB (RCC) and CXAC (SCLC), did not show efficacy in combination with standard of care (SOC) at 20-mg dose. Therefore, Lilly proposed to test higher dose levels of LY2510924 in this CXAD combination therapy setting by increasing the predefined ANC threshold criteria to 75 000. After the first patient is enrolled and receives study treatment in the 40-mg cohort, there will be a 2-week observation period, after which enrollment will continue after notification from the sponsor.

The PK/pharmacodynamic modelling based on CD34+ cells from Study CXAA indicated a plateau in the increase of CD34+ in peripheral blood for the dose levels above 20 mg but this was based on dose levels up to 30 mg only.

Durvalumab

Monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, nonclinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase 1 trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited nonlinear (dose dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life ($t_{1/2}$) with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (further information on immunogenicity, please see the current durvalumab IB).

Data from Study D4190C00006 (Phase 1 trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab every 4 weeks (Q4W) or Q2W (further information on PK observations in Study 006, please see the current durvalumab IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

A population PK model was developed for durvalumab using monotherapy data from Study 1108 (N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Ellis et al. 2008; Fairman et al. 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC at steady state (AUC_{ss}) 4 weeks). Median C_{max} at steady state ($C_{max,ss}$) expected to be higher with 20 mg/kg Q4W (~1.5-fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25-fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Fixed Dosing

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 ~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 (2009) investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). 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 PK/pharmacodynamics 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, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study given the decreased frequency of Q4W compared to Q2W regimen leading to further ease of use. Fixed dosing of durvalumab is recommended only for patients with >30 kg body weight due to endotoxin exposure.

6. Investigational Plan

6.1. Study Population

6.1.1. Screening Procedures

Patients who do not meet the criteria for participation within the 28-day screening period (screen failure) may be rescreened with the approval of the study manager (see below). Note that repeating laboratory tests during the 28-day screening period does not constitute rescreening (any test that does not meet eligibility may be repeated within the 28-day period and not considered a rescreening). Results of the repeat screening do not have to be received within the 28-day period. Screening laboratory tests may not be repeated more than twice in order to meet eligibility during the 28-day screening period. If a repeat laboratory value meets eligibility, that test must be repeated again to confirm eligibility.

After the initial 28-day screening period, a patient may be rescreened. The interval between rescreenings should be at least 1 week. If a patient does not meet eligibility within the first 28-day screening period, the patient may be rescreened beginning on Day 35. Rescreening may occur up to 2 times after the initial screening, if needed. Each time rescreening is performed, the patient must sign a new informed consent form (ICF) and will be assigned a new identification number. All required tests including laboratory tests, ECGs, and computed tomography (CT) scans with contrast must be repeated in patients who are rescreened in a new 28-day period.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted. Any missing laboratory or test results precludes patient from being enrolled on this study until those laboratory or test results are available. Local laboratories will be used to assess eligibility.

6.1.2. 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.

[1] Phase 1a: Have histologic or cytologic confirmation of advanced solid tumor (see American Joint Committee on Cancer Staging Criteria; Edge et al. 2009), and must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed to provide clinical benefit for their disease or the patient has refused available standard therapies.

[2] Phase 1b: Histologic or cytologic confirmation of advanced cancer in the following tumor types:

a) Pancreatic cancer
- Cytologically or histologically confirmed pancreatic adenocarcinoma (excluding other pancreatic malignancies [eg, acinar cell carcinomas, adenosquamous carcinomas, and neuroendocrine islet cell neoplasms])
- Metastatic disease or locally advanced, unresectable disease

- Have had disease progression, be refractory or intolerant to no more than 2 prior systemic regimens for locally advanced or metastatic pancreatic cancer. Patients who have received prior neoadjuvant therapy and who now have metastatic disease, must receive FOLFIRINOX, FOLFOX, single-agent gemcitabine, gemcitabine/nab-paclitaxel, or TS-1 (tegafur gimeracil oteracil potassium) prior to enrollment on this study.

b) Ovarian cancer

- Cytologically or histologically proven epithelial ovarian cancer (except borderline ovarian tumor histology), fallopian tube cancer, or primary peritoneal cancer with evidence of recurrence or refractory disease, which is advanced and not amenable to curative surgery or radiotherapy (International Federation of Gynecology and Obstetrics [FIGO] Staging; Odicino et al. 2008).
- Have recurrence of cancer at least 6 months after completion of first-line platinum-based therapy.
- Have received chemotherapy for recurrence of disease, but not exceeding 4 lines of therapy during which time disease may be platinum sensitive or resistant.

[3] Have at least 1 measurable lesion assessable using standard techniques by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al. 2009; Attachment 10). Positron emission tomography (PET) scans and ultrasounds may not be used for diagnostic purposes.

[4] Are ≥18 years of age.

[5] Have a minimum body weight of >30 kg.

[6] Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥9g/dL or ≥5.6 mmol/L
	Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator (at least 3 days before starting treatment with study drug). Initial treatment must not begin until 2 days after the erythrocyte transfusion and after the confirmation of hemoglobin level ≥9 g/dL.
INR or PT	≤1.5 × ULN, unless patient is receiving stable dose anticoagulant therapy (these patients are eligible as long as PT or INR is within therapeutic range of the intended use of the anticoagulant).
Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (aPTT)	PTT or aPTT ≤5 seconds above ULN, unless patient is receiving anticoagulant therapy, where the PTT or aPTT is within therapeutic range of intended use of anticoagulants.
Hepatic	
Total bilirubin	≤1.5 × ULN except patients with Gilbert's Syndrome who must have a total bilirubin level of <3.0 × ULN and will be allowed only in consultation with their physician.
ALT and AST	≤2.5 × ULN **OR** ≤5 × ULN if the liver has tumor involvement
Albumin	≥3g/dL
Renal	
Calculated creatinine clearance (see Attachment 8)	Serum creatinine CL >40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault, 1976) or by 24 hour urine collection for determination of creatinine clearance
Urine protein	<2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <2 g of protein in 24 hours to allow participation in the study.
Thyroid function	TSH OR free T4 within normal limits

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; CL = clearance; INR = international normalized ratio of prothrombin time; PT = prothrombin time; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[7] Have a performance status of 0 or 1 on the ECOG scale (refer to Attachment 7).

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

Previous Treatment	Length of Time Prior to First Dose of Study Treatment
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥2 weeks
Mitomycin-C or nitrosoureas	>42 days
Biologic agents (for example, antibodies)	≥2 weeks
Radiotherapy	≥4 weeks
Limited field radiotherapy	≥2 weeks
Major surgery, excluding biopsy	Patients with recent major surgery must have occurred >28 days prior to screening) must have recovered, in the opinion of the investigator, from the toxicity and/or complications from the intervention before starting therapy.
Study drug with an investigational product or nonapproved use of a drug or device	≥2 weeks

NOTE: At the discretion of the investigator, patients with hormone-refractory prostate cancer who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy or patients with breast cancer who are stable on anti-estrogen therapy (for example, an aromatase inhibitor) may continue that treatment while enrolled in this study.

[9] Have provided tissue from a newly obtained core or excisional biopsy of a tumor lesion or a recent biopsy defined by ≤3 years since last documented progression of disease. (Note: patients for whom newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived specimen can be submitted upon agreement from sponsor and if not restricted by local regulations.)

For ovarian expansion arm only: Be able to provide tissue (newly obtained core or excisional biopsy of tumor lesion) from an on-treatment biopsy for biomarker analysis.

[10] Are male patients who are sterile (including vasectomy confirmed by post-vasectomy semen analysis) or agree use of an effective method of contraception and not to donate sperm or practice total abstinence from heterosexual activity, starting with the first dose of study treatment, during the study, and for at least 6 months following the last dose of study treatment, or longer, if determined by country requirements;

[11] Female patients must either be of nonreproductive potential (ie, postmenopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

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

[13] Capable and willing to learn to self-administer LY2510924, or have a caregiver who is willing to learn and able to administer LY2510924 by SQ injection.

6.1.3. Exclusion Criteria

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

[14] Have a serious concomitant systemic disorder or laboratory abnormality that would compromise interpretation of results or the patient's ability to adhere to the protocol

- Including active infection with human immunodeficiency virus (HIV) (HIV 1/2 antibodies)
- Active infection with hepatitis B virus (positive hepatitis B surface antigen [+HBsAg]), or hepatitis C virus (HCV)
- Known history of previous clinical diagnosis of tuberculosis
- History of primary immunodeficiency
- Have prior or second concurrent primary malignancies that, in the judgment of the investigator and Lilly, may affect the interpretation of results. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low (such as basal cell carcinoma), as judged by the Lilly clinical research physician (CRP) or designee, are eligible for this study.
- Active autoimmune disorders, or prior documented severe autoimmune or inflammatory disorders requiring immunosuppressive treatment (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of diverticulosis, irritable bowel syndrome, or other serious gastrointestinal chronic conditions associated with diarrhea); systemic lupus erythematosus; Wegener Granulomatosis (with polyangiitis), Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion:
  - Patients with vitiligo or alopecia
  - Patients with diabetes mellitus type I or resolved childhood asthma/atopy
  - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement, or psoriasis not requiring systemic treatment

  - Any chronic skin condition that does not require systemic therapy
  - Patients with celiac disease controlled by diet alone
  - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients requiring escalating or chronic supraphysiologic doses of corticosteroids (>10 mg /day of prednisone or an equivalent corticosteroid) for control of their disease or immunosuppressive agents (eg, cyclosporine) for any reason are excluded. Patients with resolved childhood asthma/atopy are eligible. Patients who require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement, Raynaud's syndrome or Sjögren's syndrome will not be excluded from the study
- Have a bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection, either condition with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea
- Have evidence of interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity or active, noninfectious pneumonitis
- Have an active infection
- Have moderate or severe cardiovascular disease:
  - Have the presence of cardiac disease, including a myocardial infarction or any other arterial thrombotic event including cerebrovascular accident or transient ischemic attack within 6 months prior to study entry, unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, aneurysm of major vessels or heart, left ventricular (LV) ejection fraction <50% (echocardiographic evaluation based on institutional lower limit of normal performed within 28 days of first dose), or uncontrolled hypertension;
  - Have a history of QT interval prolongation, history of uncontrolled cardiac arrhythmias, congenital long QT syndrome, or who require drugs known to cause QT prolongation;

- Have valvulopathy that is severe, moderate, or deemed clinically significant; or documented major ECG abnormalities that are clinically significant at the investigator's discretion(for example, symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, bundle-branch blocks, ventricular hypertrophy, or recent myocardial infarction; or a mean QT interval corrected for heart rate (QTc) is ≥450 ms calculated using Fridericia's Correction, confirmed on triplicate ECG);

[15] Have had prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen-4 antibody (including but not limited to ipilimumab, durvalumab, or tremelimumab) or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3.

[16] Previous participation in any randomized controlled trial that included arms with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen-4 antibody (including but not limited to ipilimumab, durvalumab, or tremelimumab) or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3, irrespective of actual treatment received on the trial.

[17] Female patients who are pregnant, breastfeeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

[18] Have received a live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

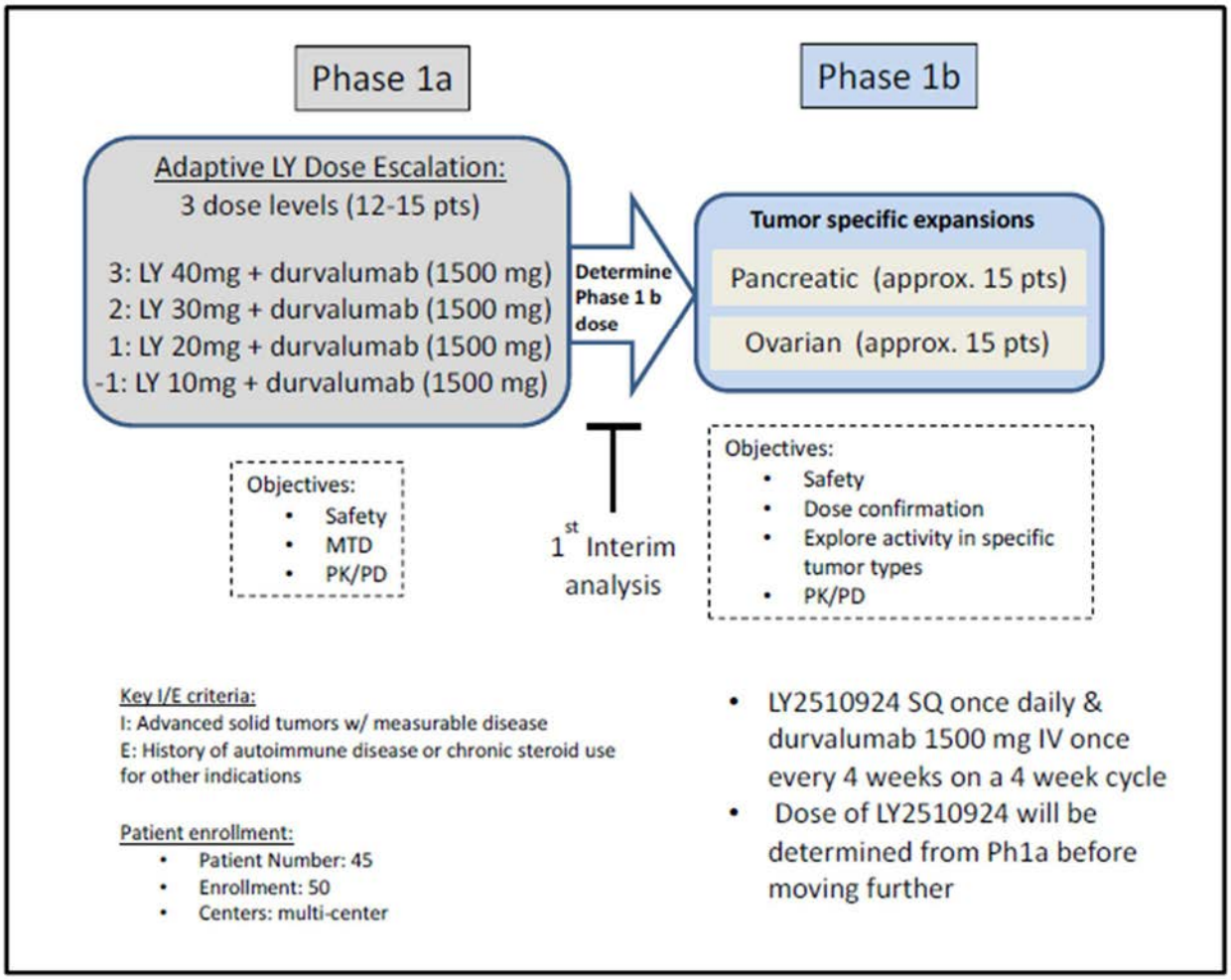
[19] Have symptomatic or uncontrolled brain metastases, spinal cord compression or leptomeningeal disease requiring concurrent treatment, including but not limited to surgery, radiation and/or corticosteroids (patients receiving anticonvulsants are eligible).

[20] Have a history of allergy or hypersensitivity to study drug components

6.2. Summary of Study Design

This is an open-label Phase 1a/1b study that will be conducted in 2 parts. The first part (Phase 1a) of the study will consist of a dose-escalation assessment of the safety and tolerability of LY2510924 administered with durvalumab (MEDI4736) with advanced refractory solid tumors (Figure CXAD.6.1). The second part (Phase 1b) of the study will be disease restricted to include 2 expansion arms in advanced pancreatic cancer (N=approximately 15 patients) and

ovarian cancer (N=approximately 15 patients), all patients receiving LY2510924 (dose determined from Phase 1a) with durvalumab. The 2 expansion arms may open either in parallel or in a staggered fashion, which will be determined after dose escalation is complete.



Abbreviations: approx. = approximately; I/E = inclusion/exclusion criteria; IV = intravenous; LY = LY2510924; Ph1a = Phase 1a; PK/PD = pharmacokinetic/pharmacodynamic; pts = patients; MTD = maximum-tolerated dose; SQ = subcutaneous.

Figure CXAD.6.1. CXAD study design.

Dose escalation for LY2510924 in combination with durvalumab in Phase 1a will be driven by an adaptive model-based dose-escalation scheme (Neuenschwander et al. 2008) to assist in the estimation of DLT rate at recommended dose levels. It provides quantitative guidance on the determination of the dose level and provides a lower under-dosing rate and a higher MTD selection rate than the traditional 3+3 method. The starting dose level will be 20 mg. Subsequent dose levels will reflect a maximum increment of 10 mg from the prior dose level. At the 40-mg dose level, the first patient will be treated and observed for 2 weeks, after which additional patients will be enrolled following notification from the sponsor. If the MTD has not yet been reached at the highest dose level of 40 mg, then additional dose levels may be

investigated based on both safety and the available PK data. Further information on the dose-escalation method is given in Section 7.2.2.

To determine the MTD of LY2510924, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacological effects using descriptive statistics and appropriate modelling techniques, if data warrant.

The actual sample size of the dose escalation (Phase 1a) will primarily be limited by the incidence of DLTs. Under the adaptive scheme, each dose level will enroll 3 patients initially (see note above on initial enrollment into the 40-mg dose level), and additional patient cohorts may be enrolled in case of DLT. The anticipated sample size for Phase 1a ranges from approximately 12 to 15 patients, depending on the incidence of DLTs. Each expansion arm in Phase 1b will enroll approximately 15 patients. The overall sample size is estimated to be approximately 45 patients.

Patients will have regularly scheduled study visits at the clinical site, including disease assessment with CT and/or magnetic resonance imaging (MRI), as appropriate (Attachment 1).

Treatment decisions related to patient management and whether to treat a patient with advanced refractory solid tumors with additional cycles of study therapy will be based on RECIST v1.1. Continuation with 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 protocol therapy and both the investigator and sponsor, in consultation with collaborator (AstraZeneca, London, United Kingdom), agree that continuing protocol therapy is in the patient's best interest. Patients will not be permitted to continue study therapy if progression occurs after confirmed response (complete response [CR] or partial response [PR] as defined by RECIST v1.1) in the target lesions (regardless of the appearance of new lesions), ie, the response and progression events both occurred in the target lesions while receiving study therapy.

At the sponsor's discretion, scans and measurements may be collected and reviewed by independent radiologists using RECIST v1.1 at a later date, or at any time during the study.

Study treatment will continue until the patient fulfills 1 of the criteria for study discontinuation (Section 6.3). Patients may continue on combination therapy beyond initial radiological disease progression in the absence of clinically significant deterioration (Section 8.3.1.2). If a patient experiences an AE that requires the patient be discontinued from durvalumab or LY2510924, the patient should be discontinued from both study drugs (Section 7.2.5).

Patients who have discontinued from combination treatment will enter the Post Discontinuation Follow-Up Period with visits at approximately 30, 60, and 90 days. If a patient has discontinued treatment for reasons other than disease progression, tumor assessments should continue every 8 weeks until confirmed disease progression occurs, initiation of a new anticancer therapy, the patient dies, or is lost to follow-up. Patients will be followed for survival at least every 12 weeks (±7 days) until death or study completion. This follow-up may occur through a phone call, email, or visit by the patient or the patient's caretaker.

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

This study will be considered complete after the final analysis (occurring no more than 12 months after last patient enters treatment) and evaluation of the primary objective and secondary objectives have been performed for the expansion arm(s) in the Phase 1b portion. Investigators will continue to follow the Schedule of Events (Attachment 1) for all patients, until notified by Lilly that study completion has occurred.

The end of trial occurs after study completion, and after the last patient has discontinued study treatment and completed the 90-day follow-up (if applicable). End of trial refers to the date of the last visit or last scheduled procedure for the last patient (includes follow-up periods).

6.2.2. Definitions of Study Periods

Terms used to describe the periods during the study are defined below:

- **Baseline/Screening:** begins when the ICF is signed, and ends at the first study treatment (defined as receiving any study drug); if no study treatment is given, baseline/screening ends with the decision not to enroll. Lasts up to 28 days.
- **Study Period:** The overall study period for Study CXAD begins the day of the first patient's first dose of study treatment and ends at overall study completion (as defined in a bullet below).
    - **Study Treatment Period:** begins with the day of the patient's first study treatment and ends the day the patient and investigator agree that the patient will discontinue study treatment (discontinuation of assigned study drug(s); Section 6.3). Individual patients who enroll in Study CXAD may continue treatment until they have confirmed progressive disease or discontinued study treatment for any other reason.
    - **Post Discontinuation Follow-Up Period**: consists of the following phases:
        - **30-Day Short-Term (Safety) Follow-Up**: begins the day after the patient and the investigator agree that the patient will discontinue study treatment and ends with the short-term follow-up visit, to occur approximately 30 days thereafter.
        - **60-Day Short-Term (Safety) Follow-Up** begins the day after the 30-day follow-up visit and lasts approximately 30 days or approximately 60 days after the patient and the investigator agree that the patient will discontinue study treatment.
        - ***90-Day* Short-Term (Safety) Follow-Up** begins the day after the 60-day follow-up visit and lasts approximately 30 days or approximately 90 days after the patient and investigator agree that the patient will discontinue study treatment.
        - ***Long-term Follow-up*** begins the day after 90-day follow-up is completed and continues until the patient's death or end of trial (approximately every 12 weeks ±7 days the patient will be contacted).

- **Study Completion** for Study CXAD: occurs after the final analysis (occurring no more than 12 months after last patient enters treatment) and evaluation of the primary objective and secondary objectives have been performed. Investigators will continue to follow the Schedule of Events (Attachment 1) for all patients, until notified by Lilly that study completion has occurred.
- **Continued Access Period:** begins after study completion and ends at End of Trial. In the continued access period, patients may continue the current study treatment after study completion, as long as they experience ongoing clinical benefit (details in Section 6.2.3).
    - Patients who are in 30-day short-term follow-up when the continued access period begins will complete the 30-day short-term follow-up visit and then discontinue from the study.
    - Patients who are in 60-day short-term follow-up when the continued access period begins will complete the 60-day short-term follow-up visit and then discontinue from the study.
    - Patients who are in 90-day short-term follow-up when the continued access period begins will complete the 90-day short-term follow-up visit and then discontinue from the study.
    - Patients who are in long-term follow-up when the continued access period begins will discontinue from the study.
- **End of Trial:** The term "end of trial" refers to the date of the last visit or last scheduled procedure for the last patient (includes follow-up periods). The end of trial occurs after study completion, and after the last patient has discontinued study treatment and completed the 90-day follow-up (if applicable).

6.2.3. Continued Access

The continued access period is defined in Section 6.2.1.

Attachment 1 presents AE/SAE data collection and the necessary continued access follow-up visits, to occur after the decision is made to discontinue from the continued access period, or when the patient starts a new anticancer therapy, whichever happens first.

6.3. Discontinuations

The reason for and date of discontinuation from study treatment will be collected for all patients. The date of discontinuation (for any of the above reasons) from study treatment is to be reported on the case report form (CRF). Patients who discontinue from study treatment 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.

6.3.1. Discontinuation of Patients Inadvertently Enrolled

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be

notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP or designee and the investigator to determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the Lilly CRP or designee agrees with the investigator that it is medically appropriate for that patient. The patient may not continue on study treatment if the Lilly CRP or designee does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP or designee to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

6.3.2. Discontinuation of Patients from Study or Study Drug

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

In addition, patients will be discontinued from the study drugs and/or from the study 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)
    - if 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, legal guardian) requests to be discontinued from the study or study drug
- 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 has confirmed evidence of progressive disease by RECIST v1.1. In the setting of disease progression, the patient will discontinue from study drug(s); however, the patient will continue to be followed on study. In the setting of unconfirmed/equivocal progression, the patient should remain on study treatment

until the next assessment period or up to 12 weeks after consultation with a Lilly physician. See Section 8.3.1.2 for additional details.

- The patient is noncompliant with study procedures and/or treatment (Section 7.6).
- The patient experiences unacceptable toxicity. Note: If the patient discontinues from 1 study drug, the patient should also discontinue from the other study drug.
- Patient has a dosing interruption of either study drug of >12 weeks.
- The patient becomes pregnant.

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

6.3.3. 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 it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

6.3.4. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges it 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

7.1.1. LY2510924

LY2510924 for Injection, 20mg/mL will be supplied as a single use sterile clear solution formulation in 2 mL glass vials. Each vial contains 1.15 mL of a 20 mg/mL LY2510924 solution. The excess solution is supplied to facilitate the withdrawal of a 20-mg unit dose. One mL will be drawn from each vial to deliver 20 mg of LY2510924. The LY2510924 drug product contains no antimicrobial preservative.

The drug product is composed of LY2510924 and the inactive ingredients sodium citrate dihydrate, citric acid monohydrate, sodium chloride, sterile water for injection with sodium hydroxide and/or hydrochloric acid used if necessary for pH adjustment. Vials of LY2510924 for Injection, 20mg/mL, must be stored refrigerated (2°C to 8°C).

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

7.1.2. Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied as a 500-mg vial solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine‑hydrochloride, 275 mM 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.

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated study 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. Durvalumab does not contain preservatives and any unused portion must be discarded.

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

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agents and planned duration of each individual's treatment to the site personnel and patient/legal representative,
- verifying that instructions are followed properly,

- maintaining accurate records of study drug dispensation, destruction, 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

This study defines 1 cycle as 4 weeks or 28 days.

LY2510924 will be self-administered prior to the start of durvalumab infusion on the days both drugs are given together.

7.2.1.1. LY2510924

In Phase 1a, LY2510924 will be self-administered SQ at rotated injection sites every day for 28 days as outlined in a dose escalation schema; in Phase 1b, LY2510924 will be self-administered SQ for 28 days at the selected Phase 1a dose.

Approximately 30 minutes prior to dose administration, the vials should be removed from the refrigerated storage area 2°C to 8°C and allowed to equilibrate to ambient room temperature prior to injection. Study drug must be administered within 6 hours after removal from the refrigerated storage area.

Doses that are missed should not be made up.

On Day 1 of Cycles 1 to 4 and Cycle 6, LY2510924 should be self-administered at the clinic (time and date recorded) **after a blood sample is taken for LY2510924 PK but prior to the start of durvalumab.** Additionally, on Cycle 1 Days 2, 15, and 16, LY2510924 should be self-administered at the clinic (time and date recorded) **after a blood sample is taken for LY2510924 PK.**

7.2.1.2. Durvalumab

Each patient will receive IV administration of durvalumab 1500 mg on Day 1 of each cycle. This administration will be given at least 30 minutes after LY2510924.

Preparation of durvalumab doses for administration with an IV bag

The preparation of infusion bags should be done under aseptic conditions by trained personnel.

A dose of 1500 mg durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 mL of durvalumab (ie, 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific patients and should not be shared between patients.

Dose administration

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 IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter.

The IV line should be flushed with a volume of IV solution (0.9% [w/v] saline or 5% [w/v] dextrose) equal to the priming volume of the infusion set used after the contents of the IV 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.

Since the compatibility of durvalumab with other IV medications and solutions, other than 0.9% (w/v) saline or 5% (w/v) dextrose, is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

Standard infusion time is approximately 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature as shown in Table CXAD.7.1.

Table CXAD.7.1. Durvalumab Hold and Infusion Times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

Abbreviation: IV = intravenous.

In the event that either preparation time or infusion time exceeds the time limits outlined in Table CXAD.7.1, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs.

On durvalumab treatment days, measure blood pressure, pulse, temperature, and respiratory rate prior to the first infusion of the day, and as clinically indicated.

- Measure blood pressure, pulse, temperature, and respiratory rate after the LY2510924 injection (but prior to the durvalumab infusion), and as clinically indicated.
- Measure blood pressure, temperature, and pulse at the following time points (based on a standard 60 (±5)-minute infusion):
    - before the start of infusion (up to 30 minutes prior)
    - during the infusion at 30 (±5) minute intervals, including when the infusion might be prolonged due to an interruption
    - at the end of infusion at 60 (±5) minutes
    - during the 1-hour post-infusion observation period, 30 (±5) and 60 (±5) minutes after the end of infusion

If the infusion takes longer than 60 minutes, then blood pressure, temperature, and pulse measurements should follow the principles described here or more frequently if clinically indicated.

A 1-hour observation period is required after all durvalumab infusions. If the patient shows no evidence of an infusion-related reaction (IRR) with the first 2 infusions of each study drug, then for subsequent infusions, no observation period is required after each subsequent infusion. In the event an IRR occurs thereafter, the 1-hour observation between infusions should be reinstituted.

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 (up to 4 hours) 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 (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the IRR is ≥Grade 3 or higher in severity, both study drugs will be discontinued.

In the event of an IRR, blood samples will be collected for both PK (durvalumab and LY2510924) and immunogenicity (durvalumab) analysis at the following time points: (i) as close as possible to the onset of the IRR, (ii) at the resolution of the IRR, and (iii) 30 days following the IRR.

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. Phase 1a Dose Escalation

The MTD of LY2510924 determined during Phase 1a will be used for Phase 1b.

Three dose levels will be investigated in Phase 1a (Figure CXAD.6.1). Dose escalation is described in Section 7.2.2.2.

Because Phase 1a is the dose-escalation part of the 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 and the Lilly study team in consultation with the collaborator.

No intrapatient dose escalation or reduction is allowed during Phase 1a.

Dose escalation will be based on the number of DLTs experienced during Cycle 1.

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

A DLT is defined as 1 of the following AEs reported during the Phase 1a DLT observation period, if considered to be definitely, probably, or possibly related to either study regimen by the investigator; and fulfills any 1 of the following criterion using National Cancer Institute (NCI) CTCAE version (v) 4.03:

1. Non-laboratory abnormalities (clinical toxicity):
    a. Any Grade 4 immune-related AE (Attachment 10)
    b. Any Grade 4 non-laboratory AE
    c. Any CTCAE Grade ≥3 QT prolongation AE
    d. Any ≥Grade 3 colitis or noninfectious pneumonitis irrespective of duration
    e. Any Grade 3 immune-related AE (excluding colitis, QT prolongation, or pneumonitis) (Attachment 10) 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
    f. Any Grade 2 pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care, including corticosteroid therapy
    g. Grade 3 toxicity lasting an extended period of time despite optimal supportive care (for example, nausea, vomiting, and diarrhea lasting >3 days; fatigue lasting >7 days)
2. Laboratory abnormalities:
    a. Any Grade 3 laboratory value if:
        i. Medical intervention is required to treat the patient, or
        ii. Associated with clinically significant symptoms. Examples include but are not limited to, ≥Grade 3 thrombocytopenia if associated with bleeding and requires platelet transfusion, ≥Grade 3 febrile neutropenia, or
        iii. The abnormality persists for >7 days (excluding amylase and lipase)
    b. Any Grade 4 laboratory abnormalities
    c. Liver transaminase elevation >8 × upper limit of normal (ULN) or total bilirubin >5 × ULN

    Note: Liver test abnormality: For HCC patients and patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by 2-fold greater than baseline and lasts for >7 days

   d. ANC >75,000/μL or ≥Grade 3 leukocytosis (leukocytes >100,000/μL) of any duration, or leukocytosis/granulocytosis causing clinical symptoms
3. Grade 5 toxicity (that is, death)
4. Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting, for example:
   a. Any toxicity that is possibly related to study treatment that requires the withdrawal of the patient from the study during Cycle 1 (including Day 15), or
   b. A delay of >14 days in initiating Cycle 2 due to persistent Grade >2 toxicities
5. Any other ≥Grade 3 toxicity, except for the exclusions listed below.

The definition excludes the following conditions:

- Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition
- 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. Note: Grade 3 or Grade 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 bleeding that requires clinically significant 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

7.2.2.2. Dose-Escalation Method

Adaptive scheme, with incorporation of a Bayesian model-based, toxicity-band method (Neuenschwander et al. 2008), will be used to assess the safety of LY2510924 given in combination with durvalumab. The Bayesian model-based, toxicity-band method incorporates the prior expectations of the dose-toxicity curve and the observed DLT data after each cohort and provides quantitative guidance on the determination of the dose level for the next cohort. The dose recommendation relies on maximizing the probability of targeted toxicity while controlling the probability of excessive or unacceptable toxicity. This method will be applied to the observed data on an ongoing basis throughout the dose escalation. The toxicity-band method will stop early if the prespecified maximum number of patients is reached or the recommended next dose level has been administered to at least 6 patients.

During the dose-escalation period, the investigators and Lilly CRP or designee in consultation with collaborator will consider the model recommendation, the observed DLT rate, and any

DLT-equivalent toxicities observed in Cycle 2 and beyond at each cohort to determine the next dose level and determine when to stop dose escalation. Safety data, in particular, DLTs, will be the primary criteria for dose escalation. In addition, if available at the time of the dose-escalation decision, PK results will be used as secondary/supporting data for dose escalation. Additional patients may, therefore, be enrolled at a specific dose level to characterize PK/pharmacodynamics. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP or designee in consultation with collaborator; the decision will be documented in writing.

The dose levels for dose escalation are provided in Figure CXAD.6.1. The starting dose level will be 20 mg. The 20-mg and 30-mg dose levels will enroll 3 patients initially. The 40-mg dose level will enroll and treat 1 patient initially. After a 2-week observation period, the additional patients will be enrolled after notification from the sponsor. For all dose levels after the initial 3 patients have been enrolled, additional patients (at that dose level) may be enrolled in case of DLT. If deemed necessary, additional dose levels may be explored after discussion between the investigator and the Lilly CRP or designee in consultation with collaborator. The toxicity-band method has the ability to accommodate additional dose levels naturally. The DLT observation period will last for 4 weeks or to the completion of Cycle 1. Additional patients will be enrolled in a cohort to achieve the minimum of 3 evaluable patients if dropouts or dose interruptions occur that result in a patient being nonevaluable for DLTs due to nonmedical reasons. Patients who withdraw from the study during the DLT observation period for reasons other than a DLT may be replaced within the same dose level. For the purpose of making decisions on dose escalation from a safety perspective, patients will be considered evaluable (DLT-evaluable population) if they have either completed the DLT-observation period (Cycle 1) and received the scheduled durvalumab dose and at least 75% of LY2510924 doses in Cycle 1 or have discontinued study treatment or study participation before completing Cycle 1 due to a DLT. If the DLT-observation period is extended to Cycle 2, patients who discontinued during Cycle 2 in the absence of DLT-equivalent toxicity will be considered evaluable for DLT assessment.

Details regarding the toxicity-band method for this study are provided in Attachment 9.

7.2.3. Phase 1b Expansion

The Phase 1b part of the study will include 2 expansion arms (pancreatic cancer [N=approximately15 patients] and ovarian cancer [N=approximately15 patients]).

Once the safety profile of all doses tested has been characterized and the MTD of combined administration of LY2510924 and durvalumab has been defined in the Phase 1a part of the study, the expansion arms will be initiated.

Treatment in the expansion arms will consist of 1500 mg durvalumab IV on Day 1 of each cycle and LY2510924 SQ daily at the dose determined in the Phase 1a part of the study. A cycle is 28 days.

Continuous evaluation of toxicity in the expansion arms will be performed throughout enrollment in the expansion arms.

7.2.4. DLT-Equivalent Toxicity

A DLT-equivalent toxicity is defined as an AE occurring during Cycle 2 and beyond in Phase 1a that would have met the criteria for a DLT if it had occurred during Cycle 1 or during any cycle in Phase 1b. The DLT-observation period will be extended to Cycle 2 if a DLT-equivalent toxicity is observed during Cycle 2 in any cohort in Phase 1a. For individual patients experiencing a DLT-equivalent toxicity, dose adjustments will be made as outlined in Section 7.2.5. At each interim analysis (as defined in Section 10.10), the rate of DLT-equivalent toxicities will be assessed. If the rate of DLT-equivalent toxicities is unacceptable (for example, a DLT-equivalent toxicity is observed in >33% patients at a given dose level), the data will be reviewed by study investigators and the Lilly CRP or designee in consultation with collaborator and a safety analysis may be triggered. If the findings indicate that a dose level does not have an acceptable safety profile for chronic (Cycle 2 or later) administration, then a lower dose level will be chosen for further investigation. This decision will be documented in writing.

7.2.5. Dose Adjustments, Delays, or Discontinuation from Study Drug

7.2.5.1. LY2510924 Dose Adjustments, Delays, and Discontinuation for Phase 1a and 1b

If a patient has an immune-related AE that requires discontinuation of durvalumab per the dose modification table in Attachment 11, both drugs should be discontinued. Once the immune-related AE has resolved to ≤Grade 1 or baseline, the investigator in consultation with the Lilly physician may resume combination treatment as indicated in Table CXAD.7.2.

7.2.5.1.1. LY2510924 Dose Adjustments and Delays

During Phase 1a, intrapatient dose escalation or reduction of LY2510924 is not allowed.

During Phase 1b, 2 dose reductions of LY2510924 are allowed (depending on the starting dose: reduce 1 dose level if available or hold if not available). Reescalation is allowed once at the discretion of the investigator. If Grade 3/4 toxicity attributed to LY2510924 occurs after 2 previous dose reductions, LY2510924 will be discontinued. If patients are discontinued from LY2510924, patients must also be discontinued from durvalumab.

No dose reduction of LY2510924 will occur for myelosuppression. Granulocytosis was observed in patients receiving LY2510924 in the Phase 1 and 2 studies. Management of granulocytosis and nonhematologic toxicity is outlined in Table CXAD.7.2 and in the durvalumab dose-modification tables within Attachment 11.

Table CXAD.7.2. Dose Adjustments of LY2510924

Event	Intervention	Dose Adjustment
Leukocytosis (ANC >75,000/µL or leukocytes >100,000/µL)	1) Interrupt LY2510924 2) Recheck WBC, ANC every 2 to 3 days until ANC decreases to <50,000/µL	Reduce 1 dose level
Injection site reaction, Grade 3	1) Interrupt LY2510924 2) Administer topical treatment as necessary	Reduce 1 dose level
Other nonhematologic toxicities meeting treatment interruption criteria described in Attachment 11	1) Interrupt LY2510924 2) Re-examine patient at least weekly until toxicity improves to ≤Grade 1 and consider restarting treatment according to the durvalumab dose-modification tables (Attachment 11)	Reduce 1 dose level

Abbreviations: ANC = absolute neutrophil cell; WBC = white blood cell.

7.2.5.1.2. Discontinuation from LY2510924

Patients with combined elevated AST/ALT AND total bilirubin values meeting discontinuation parameters as described in the DLT definition (Section 7.2.2.1) should be considered for permanent discontinuation based on clinical judgment.

If a patient has a documented CTCAE Grade ≥3 QT prolongation, the patient should be discontinued from study treatment. The investigator should consider (and may consult with a cardiologist) whether a patient with other evidence of QT prolongation, eg, QT/QTc interval ≥501 msec and/or a change of >60 msec over baseline, should also be discontinued.

If a patient experiences an AE that requires the patient be discontinued from LY2510924, the patient should also be discontinued from durvalumab.

7.2.5.2. Durvalumab Dose Adjustments, Delays, and Discontinuation for Phase 1a and 1b

Intrapatient dose escalation of durvalumab is not allowed in either Phase 1a or 1b.

If a patient has an immune-related AE that requires discontinuation of durvalumab per the dose-modification table in Attachment 11, both drugs should be discontinued. Once the AE has resolved to ≤Grade 1 or baseline, the investigator in consultation with the Lilly physician may resume combination treatment.

For AEs that are considered at least partly due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent 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 durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (Attachment 11).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related AEs during the conduct of this study. Potential immune-related AEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Patients should be monitored for signs and symptoms of immune-related AEs. In the absence of an alternative etiology (eg, infection or progressive disease) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose-modification recommendations and toxicity management guidelines for immune-mediated reactions, for IRRs, and for nonimmune-mediated reactions are detailed in Attachment 11.

7.2.5.3. Dose Delays for Reasons Not Related to Study Treatment

Dosing interruptions of either study drug of ≤1 week are also 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 CRF.

7.3. Method of Assignment to Treatment

This study is open-label for Phase 1a and Phase 1b. 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/expansion arm for each patient.

For Phase 1a, if investigators have eligible patients who have consented concurrently, more than 3 patients may be entered at a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

7.4. Blinding

Not applicable. This is an open-label study.

7.5. Concomitant Therapy

No other therapy, including routine use of growth factors or experimental medications (for example, immunotherapy or other not approved medication) will be permitted while the patients are on the study. Growth factors and erythropoietin are allowed per American Society of

Clinical Oncology or National Comprehensive Cancer Network guidelines. Granulocyte colony-stimulating factors must be discontinued at least 24 hours prior to the start of the next cycle of treatment. Transfusions are permitted. Patients may receive prophylactic steroids (such as, prednisolone, methylprednisolone or dexamethasone; see below for limits) to prevent transfusion reactions.

Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents for treatment of pancreatic cancer) will not be allowed unless outlined elsewhere. Any disease progression requiring other forms of specific antitumor therapy will necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF. Replacement hormonal therapy initiated before study entry will be allowed.

Immunosuppressive medications will not be allowed including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs, in patients with contrast allergies or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is acceptable. Patients are also permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) unless outlined elsewhere. Live attenuated vaccines within 30 days of durvalumab dosing are not permitted (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab). Inactivated vaccines, such as the injectable influenza vaccine, are permitted. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed (see Section 6.1.3).

Patients should receive full supportive care during the trial. Concomitant palliative and supportive care for disease-related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 2 weeks prior to enrollment. The potential for overlapping toxicities with radiotherapy and durvalumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving durvalumab.

All concomitant medications should be recorded throughout the patient's participation in the study.

7.5.1. Restrictions during Study

Females of childbearing potential who are sexually active with a nonsterilized male partner must use effective contraception from screening, and must agree to continue using such precautions for 6 months following the last infusion of durvalumab; cessation of birth control after this point should be discussed with a responsible physician. Male partners of a female patient must use male condom plus spermicide throughout this period. If a barrier method of contraception is

used, 2 methods must be used as outlined in Table CXAD.7.3. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Patients must use **2 acceptable methods** of effective contraception as described in Table CXAD.7.3.
- Nonsterilized males who are sexually active with a female partner of childbearing potential must use **2 acceptable methods** of effective contraception (see Table CXAD.7.3) from Day 1 and for 6 months after receipt of the final dose of durvalumab.

Table CXAD.7.3 Acceptable Methods of Contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	Combined pill Minipill Patch

[a] Also considered a hormonal method.

Patients should not donate blood while participating in this study or for 3 months after discontinuation of study treatment.

7.6. Treatment Compliance

7.6.1. LY2510924 Compliance

Patient compliance with LY2510924 will be assessed on Day 1 of each cycle (excluding Cycle 1). Compliance will be assessed by direct questioning, review of diary, and counting any returned vials. Deviations from the prescribed dosage regimen should be recorded on the CRF. On those study days that PK collection is scheduled (see Attachment 1 and Attachment 4), patients will wait to self-administer LY2510924 until they are in the clinic.

For patients who are significantly noncompliant (<75% of expected study drug taken in a visit interval), investigative sites must counsel patients on the importance of study drug compliance and drug accountability. Patients who are consistently out of the compliance range may be discontinued after discussion with Lilly CRP or designee. A Lilly representative should be contacted upon the second instance of treatment noncompliance.

The following procedures will be employed to ensure appropriate drug accountability:

- Drug accountability will be emphasized at the start-up meeting.
- Drug accountability will be monitored throughout the study.

- Each patient should be instructed to return all study drug packaging and unused material to the study site at each visit. The study site will keep a record of all drug dispensed to and returned by the patients throughout the study. Study site personnel will return or destroy (as requested) all unused study drug for all patients.
- In the Phase 1a and 1b part of the study, patients will keep a study diary for the entire treatment duration to document that they are taking LY2510924 as prescribed.

7.6.2. Durvalumab Compliance

Durvalumab will be administered intravenously 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 CRF.

7.6.3. Evaluable Phase 1a Patients

For Phase 1a, any patient who discontinues from the study for nonmedical reasons before completing the first cycle of study treatment will be deemed nonevaluable for assessment of a dose level and may be replaced within the same dose level, unless they experience a DLT prior to withdrawal. If the patient is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered nonevaluable and may be replaced. Nonevaluable patients may be replaced to ensure that 3 patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

For the purpose of making decisions on dose escalation from a safety perspective, patients will be considered evaluable if:

- they have either completed the DLT observation period (Cycle 1) and
- they have received the scheduled durvalumab dose in the first cycle, and
- they took at least 75% of the cohort-specified doses of LY2510924

OR

- they discontinued study treatment or study participation before completing Cycle 1 due to a DLT

Patients who are not evaluable for PK, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP or designee to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

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

8.1. Safety Evaluations

Safety is the primary endpoint of this Phase 1a/b study as determined by the NCI CTCAE v 4.03. All patients who receive at least 1 dose of LY2510924 or durvalumab will be evaluated for safety as measured by the occurrence of AEs, SAEs, deaths, and laboratory abnormalities, assessed during treatment and for 90 days in follow-up.

Patients will have regularly scheduled study visits at the clinical site as noted in Attachment 1, where safety assessments including AE collection, laboratory assessments, vital sign collection, and physical examinations will be performed.

Imaging studies will be performed every 8 weeks or sooner if clinically indicated. Liver function, as part of the routine clinical chemistry panel, will be tested every other week in Cycle 1 and every cycle thereafter.

Study procedures and their timing are described in the Study Schedule (Attachment 1). 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 before completing the study. The patient should be followed 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. 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 CXAD.8.1 presents a summary of AE and SAE reporting guidelines. Table CXAD.8.1 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 subject 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 sign measurements, and so on, which 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 v 4.0.

The NCI-CTCAE v 4.0 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 v 4.0. Any minor version of CTCAE v 4.0 (for example, v 4.03) may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI CTCAE v 4.1 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 CRF. 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.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug(s) must be stopped immediately.

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 dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF the circumstances and data leading to any such dosage reduction or 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, or study drug via CRF.

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

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 therapy or other protocol-required procedure) should not be considered SAEs.

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 in offspring of the patient
- 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.

SAEs due to disease progression, including death, should not be reported as SAEs 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.

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 Drugs

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the ICF. For patients who do not enroll in the study (that is, have not received at least 1 dose of LY2510924 or durvalumab), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug to when the decision to discontinue the patient from study treatment is made.

8.1.2.2.3. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the 30-day, 60-day, and 90-day safety follow-ups occurring after last dose of combination treatment must be reported to Lilly or its designee (Attachment 1).

Following the 30-, 60-, and 90-day follow-up assessments, patients who discontinue from study treatment for progressive disease will be followed only for survival, unless there is an ongoing AE or SAE that is possibly related to study drug or protocol procedures. In this instance, the patient should be followed in subsequent follow-up visits 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. For patients who have discontinued study treatment for reasons other than progressive disease, these patients will be followed for survival, progression-free survival (PFS), time and duration of response, and best overall response (BOR), unless they have started another treatment. In that case, the patient will only be followed for survival. Patients with an ongoing AE or SAE that is possibly related to

study drug or protocol procedures will be followed until the event is resolved, unless a new treatment is started.

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 90-day follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the 90-day follow-up visit, 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, the investigator should report the SAE to the sponsor, and the SAE will be entered in the in the Lilly Safety System.

8.1.2.3. Adverse Events of Special Interest for Durvalumab

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the durvalumab safety profile and require close monitoring and rapid communication by the investigator to the sponsor. Durvalumab AESIs may be serious or nonserious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab 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 AE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternative etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an immune-related AE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-related AE.

If the Investigator has any questions in regards to an AE being an immune-related AE, the Investigator should promptly contact the study CRP or designee.

AESIs observed with durvalumab include:

- colitis
- pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- neuropathy / neuromuscular toxicity (ie, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- endocrinopathy (ie, events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- dermatitis
- nephritis

- pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- infusion-related reactions

Further information on these risks (eg, presenting symptoms) can be found in Attachment 11 and in the current version of the durvalumab IB.

8.1.2.4. Reporting Adverse Events of Special Interest

AESIs require close monitoring and rapid communication to the sponsor.

Details regarding reporting of IRRs and hepatic function abnormalities are presented in Attachment 11.

Attachment 11 presents the dose-modification guidelines and guidance for management of AESIs for durvalumab AESIs. Contact the Lilly CRP or designee if questions arise concerning AESIs.

8.1.2.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are not listed in the Development Core Safety Information (LY2510924 IB Section 7) or Summary of Data and Guidance for Investigator (durvalumab IB Section 6) 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.

8.1.2.6. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table CXAD.8.1.

Table CXAD.8.1. Adverse Event and Serious Adverse Event Reporting Guidelines for Study CXAD

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)[a]	Preexisting conditions All AEs All SAEs	x x x	 x
On therapy (Starts at first dose of study drug(s) and ends on the date the decision to discontinue the patient from study treatment is made	All AEs All SAEs	x x	 x
Follow-up visit (Starts just after the date the decision to discontinue the patient from study treatment is made and ends when end of study safety assessments are completed [30, 60, and 90 days for short-term follow-up])	All AEs All SAEs	x x	 x
Continued access period	All AEs All SAEs	x x	 x
Continued access period follow-up (30-, 60-, and 90-day continued access period follow-up)	All AEs All SAEs	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s), or protocol procedures All SAEs related to protocol procedures or study drug	x 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.

[a] If patients are not enrolled into the study (that is, have not received at least 1 dose of LY2510924 or durvalumab), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

For each patient, 12-lead digital triplicate ECGs 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. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. The mean QT interval must be calculated using a corrected heart rate calculated from 1 baseline ECG using Fridericia's Correction and confirmed with the 2 additional baseline ECGs.

ECGs 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.

ECGs 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 from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory will then conduct a full over-read on 1 of the replicates (including all intervals) and **QT/HR/RR in the other 2 replicates.** A report based on data from this over-read (confirmed ECG report) and any clinically significant findings will be issued to the investigative site. All data from the central ECG vendor's over-reads will be placed in the Lilly database for analytical and study report purposes.

It is recognized that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report-writing purposes.

The investigator (or qualified designee) must document his/her review of 1 of the replicate ECGs printed at the time of collection, the final over-read ECG report issued by the central ECG laboratory, and any alert reports.

QT prolongation that meets CTCAE Grade ≥3 criteria will be considered a DLT criterion in the Phase 1a portion of this trial; in the other parts of the study, this should be considered grounds for early withdrawal or discontinuation based on the investigator's assessment. The investigator should consider the significance of other measures of QT prolongation and may wish to consult with a cardiologist to determine whether such AEs should be reported as an SAE or should result in withdrawal of the patient from the study.

8.1.3.2. Echocardiography

Echocardiography is required at baseline to document initial LV function (Attachment 12). Additionally, echocardiography may be performed on-study as clinically indicated to determine LVEF/LV dysfunction and any change in cardiac size or function.

Echocardiography will be locally assessed (within 28 days of Cycle 1 Day 1) by individuals who are qualified by experience or training. Individuals so qualified should be identified at each site. The same person should be responsible for reading the echocardiography on any individual study patient.

8.1.4. Safety Monitoring

The Lilly CRP or designee 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. The Lilly CRP or designee will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist, and periodically review:

- trends in safety data,
- laboratory analytes,
- AEs, including monitoring of AESIs
- DLTs and DLT-equivalent AEs
- If a study patient experiences elevated alanine aminotransferase (ALT) ≥5X upper limit of normal (ULN) and elevated total bilirubin ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator.

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 or designee regarding collection of specific recommended clinical information and follow-up laboratory tests (Attachment 3).

8.1.5. 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.

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

Attachment 4 lists the PK, pharmacodynamic, immunogenicity, and biomarker sampling schedule.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood samples will be collected to determine whether patients meet inclusion/ exclusion criteria and to monitor patient health.

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/Pharmacodynamics

PK and pharmacodynamic samples will be collected as specified in the Pharmacokinetic and Pharmacodynamic Sampling Schedule (Attachment 4).

8.2.2.1. Pharmacokinetic Samples

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

Blood samples to determine LY2510924 and durvalumab PK will be collected at times specified in Attachment 4.

Blood samples will be drawn from all patients for the assessment of LY2510924 in plasma and durvalumab concentrations in serum (also known as bioanalytical samples). A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and the sponsor.

Sampling times were selected to coincide with expected C_{max} and minimum serum concentration (C_{min}) and any additional PK analysis, and with consideration to draw minimum volume of blood from patients and ensure that the patients do not need to make an extra visit to provide these samples.

Instructions for the collection and handling of bioanalytical blood samples will be provided by the sponsor. The actual date and time of LY2510924 administration must be recorded on the patient diary then reported on the CRF on the dates of interest (the most recent dose administration date and time: 1) prior to predose blood draw for PK, 2) prior to the first post-dose sample, 3) after the 24-hour sample must be recorded on eCRF). In case of additional PK collected date and time of the dose administered prior to that draw should be recorded on the eCRF.

The actual start and end date and time of durvalumab infusion administration must be recorded on the eCRF. The actual date and time that each bioanalytical blood sample was drawn must be recorded on the laboratory accession page after the sample is drawn.

LY2510924 concentrations in plasma and durvalumab concentrations in serum samples will be measured using a validated assay methodology at a laboratory designated by the sponsor.

The remaining plasma from the bioanalytical samples collected for LY2510924 PK may be pooled and used for exploratory metabolism work as deemed appropriate.

8.2.3. Samples for Tailoring and Pharmacodynamic Biomarkers

Blood and tissue samples will be collected for biomarker research in this study.

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

- blood samples (plasma, serum and whole blood) (see Section 8.2.3.1 and Section 8.2.4)
- tumor tissue (see Section 8.2.3.2)
  - a newly obtained core or excisional biopsy of a tumor lesion or a recent biopsy defined by ≤3 years since last documented progression of disease. If a fresh biopsy is obtained, an archival specimen, if available should also be submitted for comparison (see Section 8.2.3.2).
  - newly obtained biopsy specimens collected during the study treatment period (see Section 8.2.3.2) (Phase 1b ovarian expansion arm only).

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

- newly obtained biopsy specimens collected during the study treatment period (Phase 1a and pancreatic expansion arm in Phase 1b).

Sample collection including blood (plasma, serum, and whole blood) and tumor tissue will occur at specified time points as indicated in Attachment 4, where local regulations allow these samples are also described in the following sections.

It is possible that biomarker data has already been generated from samples that were collected and analyzed prior to enrolling in this trial. These data may have been generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in following sections.

8.2.3.1. Blood Samples

Blood (plasma, serum, and whole blood) will be collected and may be used for research related to, but not limited to the drug targets, immune cells/immune functioning within disease state and cancer-related conditions, pathways associated with cancer and study drugs, variable response to LY2510924 and/or durvalumab, the mechanism of action of LY2510924 and/or durvalumab, and/or research methods or in validating diagnostic tools or assay(s) related to cancer. Potential pharmacodynamic and/or circulating markers may include, but not limited to: PD-L1+ cells,

CD34+ stem cells and total white blood cells as well immune cell subsets characterization. Blood will be collected at times specified in Attachment 4. All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples may be stored for a maximum of 15 years following last patient visit for the trial or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

8.2.3.2. Tumor Tissue

Tissue collection will be required for biomarker research and enrollment into the study. To meet study eligibility criteria, and therefore mandatory for study participation, patients must have available tissue from a newly obtained core or excisional biopsy of a tumor lesion or a recent biopsy defined by ≤3 years since last documented progression of disease will be required. If a fresh biopsy is obtained, an archival specimen if available should also be submitted for comparison if not restricted by local regulations. In addition, newly obtained biopsy collected during the study treatment period is required if any accessible lesions remain (mandatory in Phase 1b ovarian expansion arm only, optional in Phase 1a and pancreatic expansion arm in Phase 1b). For patients for whom newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived specimen can be submitted upon agreement from Sponsor. Pre- and on-treatment assessments are critical for meaningful clinical data, paired biopsies are planned to be tested from baseline over time for changes in molecular markers to document any potential immunomodulatory activity of treatment in patients with LY2510924 and durvalumab and should be performed if clinically feasible.

Pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue should be in a whole block or unstained slides. Blocks will be sectioned and returned to the site. Slides will not be returned.

In addition to the biopsies and biomarker samples discussed in Sections 8.2.3.1 and 8.2.3.2, 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 only be performed 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. Cytological or fine-needle aspiration specimens 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. Each sample will be labeled with patient number and tissue of origin and be stored for up to 15 years after the last patient visit at a facility selected by the sponsor.

Tumor tissue will be examined for biomarkers related to, but not limited the drug targets, disease process, immune cells/immune functioning within the disease state, and cancer-related conditions, pathways associated with cancer and study drugs, mechanism of action of LY2510924 and/or durvalumab, and/or research methods or in validating diagnostic tools or assays.

Gene expression, sequencing 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, microenvironment and changes in stromal and tumor biology in response to study treatment. The results of this analysis may be correlated with clinical efficacy data.

The samples and any data generated from them can only be linked back to the patient 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.

8.2.4. 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 only be used 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 for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient 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.

8.2.5. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine ADA production against durvalumab. The specific time points are listed in Attachment 4. Sample collection, storage, and shipment instructions for blood samples will also be provided in the Central Laboratory Manual. Pretreatment and post-treatment samples will be collected and assayed for

the presence of ADA using an immunoassay. The number and percentage of patients with positive antidrug response will be summarized. In the event of a study treatment-related infusion reaction, every effort should be made to collect blood samples for anti-durvalumab antibody determination, as well as blood samples for durvalumab serum concentration, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

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

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 radiologic tests for tumor measurement:

- CT scan
- MRI

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

- Tumor measurement by RECIST v1.1 (Eisenhauer et al. 2009; Attachment 10).
- Evaluation of tumor markers, if indicated.
- Evaluation of performance status (refer to the ECOG scale, Attachment 7).

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated for subsequent imaging, using the sample method that was used at baseline.

8.3.1. RECIST Version 1.1 with Confirmatory Scan for Disease Progression

8.3.1.1. Rationale for RECIST Version 1.1 with Confirmatory Scan for Disease Progression

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

- Response to immunotherapy may be delayed.
- Response to immunotherapy may occur after progressive disease by conventional criteria.
- The appearance of new lesions may not represent progressive disease with immunotherapy.
- Stable disease (SD) while on immunotherapy may be durable and represent clinical benefit.

Therefore, to adequately characterize additional patterns of response and progression specific to patients treated with immunotherapy, which cannot be captured by conventional criteria such as RECIST v1.1, alternative measures of tumor assessment have been developed: 1) RECIST v1.1 with confirmatory scan for disease progression and 2) immune-related response criteria (irRC, Wolchok et al. 2009). For both measures 1) and 2) clinically stable patients may continue treatment until disease progression (per standard RECIST v1.1) is confirmed. As the irRC are still being developed and validated for various tumor types, Study CXAD will use RECIST v1.1 with confirmatory scan for disease progression, which may discourage the early discontinuation of study treatment and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria.

Table CXAD.8.2 provides an overall comparison across the 2 measures of disease progression to be used in Study CXAD, and irRC.

Table CXAD.8.2. Summary of Response Assessment by RECIST, RECIST with Confirmatory Scan for Progressive Disease, and irRC

	Used in Study CXAD		Not Used in Study CXAD
Definition	**RECIST v1.1**	**RECIST v1.1 with confirmatory scan for PD**	**irRC (Wolchok et al. 2009)**
New lesion	The presence of new lesion defines progression	The presence of new lesion defines progression	The presence of new lesion does not define progression The measurements of the new lesion(s) are included in the sum of the measurements
Confirmation of PD	Not required	PD, in the absence of clinically significant deterioration, requires confirmation with repeat imaging after ≥4 weeks. After initial PD following RECIST v1.1, shift to "RECIST v1.1 with confirmatory scan for PD."	Required

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

8.3.1.2. Application of RECIST Version 1.1 with Confirmatory Scan for Disease Progression

For Study CXAD, based on the unique response to immunotherapy and guidelines from regulatory agencies (for example, the European Medicines Agency's "Guideline on the evaluation of anticancer medicinal products in man" [EMA/CHMP/205/95/Rev.4] for immune modulating anticancer compounds), the following will be applied, in addition to standard RECIST v1.1 criteria:

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

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

- In the case of clinically significant deterioration, the patient will discontinue study treatment (Section 6.3.2).

- For patients who continue to receive clinical benefit, and in the absence of clinically significant deterioration despite evidence of objective progressive disease with the confirmatory scan, the patient may continue study treatment at the discretion of the investigator, in consultation with the Lilly CRP or designee. Patients with a decline in ECOG performance status to >1 will not be permitted to continue study treatment after confirmed progression of disease.

NOTE: In determining whether or not progression can be confirmed, the site study team should consider all target lesions, nontarget lesions, and new lesions. Patients will not be permitted to continue study therapy if progression occurs after confirmed response (CR or PR as defined by RECIST v1.1) in the target lesions (regardless of the appearance of new lesions), ie, the response and progression events both occurred in the target lesions while receiving study therapy.

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 samples, 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 CRF.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study.

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 CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

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 institutional review board (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.

CRF data collected by the third-party organization (TPO) will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to Lilly data warehouse, using standard Lilly file transfer processes. For any data handled by the sponsor internally, it will be managed by the sponsor and stored electronically in the sponsor's data warehouse.

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.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-

reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Attachment 5 contains a data sharing and sample testing schedule for this study.

9.2.2. Ancillary Data

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly data warehouse and TPO's system.

ECG data will be stored electronically in the central database system of Lilly's central review organization. Data will subsequently be transferred from the central review organization system to the Lilly data warehouse and TPO's system.

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 45 patients may be enrolled in this multicenter, open-label Phase 1a/1b study. Patients will be enrolled into the Phase 1a cohorts sequentially without randomization to dose. The Bayesian model-based, toxicity-band method will be followed to assist dose escalation during Phase 1a. The toxicity-band method will provide quantitative guidance on the determination of the dose level for the next cohort based on the observed DLT data. Compared with the traditional 3+3 method, the toxicity-band method provides a lower under-dosing rate and a higher MTD selection rate, with a well-controlled overdosing rate at a prespecified criterion. Refer to Attachment 9 for more details. The sample size for Phase 1a will primarily be determined by the incidence of DLTs. The anticipated sample size for Phase 1a ranges from approximately 12 to 15 patients. The sample size of approximately 15 patients per tumor type in the Phase 1b expansion arm has been selected to allow adequate assessment of safety at the recommended dose level. It 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 (CI) are summarized in Table CXAD.10.1. The values are provided as a reference for estimation rather than a basis of any decision criteria. The MTD may be revised based on the safety data obtained in Phase 1b (Iasonos and O'Quigley 2013).

Table CXAD.10.1. Estimated Incidence Rate and Its Two-Sided 95% Confidence Interval

Number of Cases (N=15)	Estimated Incidence Rate	95% Confidence Interval[a]	
		Lower Limit	Upper Limit
0	0.0	0.0	0.22
3	0.2	0.04	0.48
6	0.4	0.16	0.68
9	0.6	0.32	0.84

Abbreviation: N = number of patients.

[a] 95% Clopper-Pearson interval for binomial distribution with sample size of 15.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company.

The analyses for this study will be descriptive; no p-values will be calculated. Data analyses will be provided by cohorts/expansion arms and for all study patients combined whenever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, percentages, and their standard errors. Also, 95% CI will be constructed for the estimates if appropriate. Missing data will not be imputed.

The interpretation of the study results will be the responsibility of the investigator along with the Lilly CRP or designee, pharmacokineticist, and statistician. The CRP or designee 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.

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

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/or listing of the following:

- Patient demographics including, for example, age, sex, ethnicity/race, weight, and screening body mass index (BMI) will be reported.
- 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 1 dose of either study drug will be evaluated for safety and toxicity. AE terms and severity grades will be assigned by the investigator using CTCAE, version 4.03).

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug, and concomitant medications
- dose adjustments
- laboratory values
- vital signs and physical examinations
- DLTs at each dose level
- ECGs

10.5. Pharmacokinetic Analyses

PK analyses will be conducted on patients who have received at least 1 dose of the study drugs and have had samples collected.

PK parameter estimates for LY2510924 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be AUC of LY2510924. Other noncompartmental parameters, such as time of $t_{1/2}$, CL/F, and apparent volume of distribution (V/F) may be reported.

Summary statistics will be tabulated for the PK parameters of durvalumab.

Population PK analyses for LY2510924 and/or durvalumab may be conducted using a population PK approach. The relationship between LY2510924 and/or durvalumab exposure and selected safety outcomes, pharmacodynamics/biomarkers, and immunogenicity may be explored, if necessary.

10.6. Biomarker Analyses

Exploratory biomarkers will be summarized and assessed for correlations with clinical outcomes. Biomarker relationships by tumor type, changes in biomarker levels at baseline and over time, and differences among dose levels or exposure will be explored as possible.

The pharmacodynamic effect from all patients undergoing pharmacodynamic assessments will be explored.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

PK/pharmacodynamic analyses for LY2510924 may be conducted as deemed necessary by Global PK/ pharmacodynamic 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. Immunogenicity

Immunogenicity incidence will be tabulated, and correlation to durvalumab, 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.

10.9. Efficacy

Tumor response data will be provided by cohort/expansion arm (according to RECIST v1.1). Particularly, the antitumor effect will be summarized by best overall response, including the overall response rate (ORR) and disease control rate (DCR). A patient is considered to have a tumor response if they achieve a confirmed CR or PR. The ORR will be estimated by dividing the total number of confirmed complete and partial responders (CR+PR) by the total number of enrolled patients. The DCR will be estimated by dividing the total number of CR+PR+SD by the total number of enrolled patients. A 95% exact CI will be constructed to determine the level of precision of the ORR and DCR. Time-to-event variables such as PFS, time to response, duration of response and overall survival will be tabulated, and the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves, medians, and survival rates (eg, 6-month survival rate) if applicable.

10.10. Interim Analyses

Data will be reviewed on a cohort-by-cohort basis during Phase 1a of the study, until the MTD is determined. The purpose of these cohort-by-cohort reviews is to evaluate the cumulative safety data (Cycle 1 and all later cycles) at each dose level(s) that has/have enrolled study patients, and

determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team in consultation with collaborator 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.

Once MTD is determined for Phase 1a, an interim analysis will be performed prior to opening Phase 1b.

In Phase 1b, if a DLT-equivalent toxicity occurs in one-third or more of patients during Cycle 1 (with a minimum of 6 patients enrolled), a data review will be performed to determine whether to continue at the current LY2510924 dose or whether the dose of LY2510924 should be reduced. If the DLT-observation period is extended to 2 cycles during Phase 1a, this analysis will also include DLT-equivalent toxicities occurring in Cycle 2.

In Phase 1b, a safety review may occur for each expansion arm approximately 2 months after approximately 8 of the planned patients per arm start study therapy.

If an unplanned interim analysis is deemed necessary, the sponsor will determine if it is necessary to amend the protocol.

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

The final analysis and evaluation of the primary objective and the secondary objectives will be performed no more than 12 months after the last patient of each expansion arm starts study therapy, and the final analysis may be conducted separately for each expansion arm. A clinical study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK, and pharmacodynamic biomarkers.

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.

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.

11.2. Ethical Review

The sponsor or its representatives must approve all ICFs before they are used at investigative sites. 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.

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

- the current IB 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 enrolled 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.

12. References

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Attachment 1. Protocol CXAD Study Schedule

Baseline, During and Poststudy Assessments

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.
Visits							**801**	**802**	**803**	**804**	
Informed Consent	x										Informed Consent Form signed (prior to performance of any protocol-specific tests/procedures).
Medical History	x										Including alcohol/tobacco use and other relevant habits assessments.
Physical Examination/ Vital Signs	x		x		x	x					Full examination at baseline. Focused examination at other time points. During the study treatment period, occurs within 3 days prior to first day of each cycle. Includes recent height (baseline only), weight, and vital signs (blood pressure, pulse, temperature, and respiratory rate [at baseline and as indicated in Section 7.2.1.2]). See Section 7.2.1.2 for a detailed description of vital sign collection on study.
ECHO	x										Local. ECHOs may be performed on study as clinically indicated to determine LVEF/LV dysfunction and any change in cardiac size or function.

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.
Visits							**801**	**802**	**803**	**804**	
ECG		x	x	x	x						**Obtain ECGs before any associated blood draws.** At baseline, triplicate ECG will be obtained, on which QTcF must be <450 ms (calculated from one ECG using Fridericia's Correction Formula and confirmed with 2 additional ECGs). Cycle 1 Day 1: ECG will be conducted 30 mins **post** LY2510924 dose. Cycle 1 Day 15 and Cycle 2 Day 1: ECGs will be conducted **predose**. All ECGs will be done in triplicate.
Concomitant Meds	x		x		x	x	x	x	x		Throughout study as needed.
ECOG Performance Status	x		x		x	x	x	x	x		
HIV, Hepatitis B, and Hepatitis C Testing	x										All tests completed locally. Hepatitis B (HBsAg, Anti-HBc) Hepatitis C (Anti-HCV, HCV RNA)
Hematology		x	x	x	x	x	x	x	x		Local. Complete blood count with differential. If any abnormalities, will follow beyond the 30-day FUP, as clinically indicated

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.
Visits							**801**	**802**	**803**	**804**	
Serum Chemistry and Liver Function Testing		x	x	x	x	x	x	x	x		Local and central. See Attachment 2. If any abnormalities, will follow beyond the 30-day FUP, as clinically indicated. To include liver enzyme panel.
Tumor Markers in Blood	x		x		x	x	x	x	x		Local. If applicable to tumor type of the patient (eg, CEA in patients with colorectal cancer or CA125 in patients with ovarian cancer). Obtain predose, if dose administered.
Coagulation		x									Local. Includes prothrombin time, aPTT and INR. As clinically indicated on study and prior to any procedures (eg, tumor biopsy).
Thyroid Function Tests		x	x		x	x	x	x	x		Local. Includes TSH and fT4. Additionally, measure if there is clinical suspicion of an adverse event related to the endocrine system.
Urinalysis		x	x		x	x	x	x	x		Local. See Attachment 2. If any abnormalities, will follow beyond the 90-day FUP, as clinically indicated.
CTCAE v 4.03 Grading		x	x	x	x	x	x	x	x	x	To be reported only after study eligibility is confirmed. Throughout study as needed. Refer to Section 8.1.2.6 for reporting guidelines. Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Urine or Serum Pregnancy Test		x									Local. As clinically indicated while on study.

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.
Visits							**801**	**802**	**803**	**804**	
Tumor Tissue	≤3 yrs prior				D7						Central. Core or excisional biopsy of a tumor lesion or a recent biopsy defined by ≤3 years since last documented progression of disease. Patients for whom newly obtained samples cannot be obtained such as in cases of inaccessibility or patient safety concern, an archived specimen can be submitted upon agreement from sponsor. If a fresh biopsy is obtained, an archival specimen (if available) should also be submitted for comparison. On-treatment sample (Cycle 2 Day 7 ±7 days): mandatory for ovarian expansion arm (Phase 1b), optional in Phase 1a and pancreatic expansion arm in Phase 1b.
PK Sampling			D1 & 2	D15 & 16	x	C3, C4, & C6			x		See PK Sampling Attachment 4 for exact timing.
Serum, Plasma, and Whole Blood Samples for Biomarkers		x	See Attachment 4 for exact timing.				x				Baseline sample for whole blood only, and must be collected ≤7 days prior to Cycle 1 Day 1. See Attachment 4 for exact timing.
Radiological Tumor Assessment	x				x		x				Local. CT scans will begin within 7 days prior to starting Cycle 3 and every other cycle afterwards including follow-up (approximately 8 weeks apart).

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.
Visits							**801**	**802**	**803**	**804**	
Blood for pharmaco-genetics		x									It is highly recommended to draw the whole blood sample on Cycle 1 Day 1 prior to the first dose; however, it can be collected later during the study if necessary.
Other safety or laboratory assessments; for example, immuno-genicity					x	C4			x		Note: Day 1 sample should be taken prior to durvalumab and LY2510924.
Survival/ subsequent anticancer therapy							x	x	x	x	At long-term FUP, at least every 12 weeks ±7days until patient's death or study completion.
Durvalumab			x		x	x					In clinic on Day 1 of each cycle.
LY2510924			Days 1-28		Days 1-28	Days 1-28					LY2510924 will be self-administered SQ daily. On Cycle 1 Days 1, 2, 15 and 16 and on Cycles 2 to 4 Day 1, LY2510924 should be taken at the clinic (time and date recorded) after a blood sample is taken for LY2510924 PK but prior to the start of durvalumab (refers to Day 1 of each cycle only).
Dispense study drugs and assess compliance			x		x	x					Collect drug diary prior to dispensing study drug for cycle.

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.
Visits							**801**	**802**	**803**	**804**	
Dispense/ collect patient diaries			x		x	x					Patients will complete diaries once per cycle.

Abbreviations: aPTT = activated partial thromboplastin time; C = cycle; CEA = carcinoembryonic antigen; CT = computer tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FUP = follow-up HBsAg = hepatitis B surface antigen; HBc = hepatitis B core antibody; HCV =hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio of prothrombin time; LTFU = long-term follow-up; n = cycle number; LV = left ventricular; LVEF = left ventricular ejection fraction; PK = pharmacokinetic; QTcF = Fridericia's formula corrected QT interval; RNA = ribonucleic acid; SAE = serious adverse event; SQ = subcutaneous; TSH = thyroid-stimulating hormone; yrs = years.

[a] Long-term follow-up begins the day after the 90-day follow-up is completed and continues until the patient's death or end of trial (approximately every 12 weeks ±7 days the patient will be contacted).

Continued Access and Post Continued Access Assessments

	Cycle n	Follow-Up (days)[a]			Comments
Relative Day Within a Cycle	**1**	**30**	**60**	**90**	
Visit	**501-5XX**	**901**	**902**	**903**	
CTCAE v 4.03 grading	x	x	x	x	To be reported only after study eligibility is confirmed. Throughout study as needed. Refer to Section 8.1.2.6 for reporting guidelines. Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Durvalumab	x				In clinic on Day 1 of each cycle. Patients will continue to receive study drug(s) at the same dose and schedule as when in the main study.
LY2510924	x				LY2510924 will be self-administered SQ daily.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; n = cycle number; SAE = serious adverse event; SQ = subcutaneous.

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

Attachment 2. Protocol CXAD Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[b]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Mean corpuscular hemoglobin	Magnesium
Mean corpuscular hemoglobin concentration	Chloride
Mean corpuscular volume	Phosphorus
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total and direct bilirubin
Neutrophils[c] (% and absolute)	Alkaline phosphatase
Lymphocytes (% and absolute)	Alanine aminotransferase
Monocytes (% and absolute)	Aspartate aminotransferase
Platelets	Bicarbonate
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
	Total protein
Coagulation[b]	Calcium
aPTT	Glucose, random
PT	Albumin
INR	
Urinalysis[b]	**Clinical Chemistry**[d]
Bilirubin	**Serum Concentrations of:**
Blood	Lactate dehydrogenase (LDH)
Color and appearance	Lipase
Glucose	Gamma glutamyl transferase (GGT)
Ketones	Creatine kinase
pH	Amylase
Protein	
Specific gravity	**Thyroid Function Tests**[b]
Urine leukocyte esterase	Thyroid stimulating hormone
	Free thyroxine (fT4)
	Hepatitis B (HBsAg, Anti-HBc)[b]
	Hepatitis C (Anti-HCV, HCV RNA)[b]
	HIV[b]
	Urine or serum (β-human chorionic gonadotropin (β-hCG) **Pregnancy Test** (females only)[b]

Clinical Laboratory Tests

Abbreviations: aPTT = activated partial thromboplastin time; CRF = case report form; HBsAg = hepatitis B surface antigen; HBc = hepatitis B core antibody; HCV =hepatitis C virus; INR = international normalized ratio of prothrombin time; PT = prothrombin time; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

[a] Local chemistry laboratory testing will be used to determine patient eligibility and decisions for treatment. Central chemistry laboratory testing will also be performed, and will be used for data analyses.

[b] Local or investigator-designated laboratory. Treatment decisions will be based on local laboratory results.

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

[d] Centrally only.

Attachment 3. Protocol CXAD Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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 or designee regarding collection of specific recommended clinical information and follow-up laboratory tests.

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 or designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Activated partial thromboplastin time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-Actin antibody**
AST	**Anti-nuclear antibody[a]**
GGT	**Anti-smooth muscle antibody[a]**
CPK	

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

[a] Assayed by Lilly-designated laboratory.

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

Attachment 4. Protocol CXAD Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Biomarker Sampling Schedule

Pharmacokinetic (PK) samples will be collected for both LY2510924 and durvalumab and immunogenicity (IK) samples will be collected for durvalumab only. Predose sample for LY2510924 should be drawn as close as possible prior to the subcutaneous (SQ) injection of LY2510924, and that for durvalumab should be drawn as close as possible prior to start of durvalumab infusion (but can be drawn up to 1 hour or 60 minutes prior to the start of infusion). All post-dose blood draws for LY2510924 PK should be drawn in the preferred time windows listed in the table below. Exact clock reading for the time of blood draw should be recorded. While best effort should be done to draw the blood sample within the time window provided, it is more important to ensure that the predose sample for LY2510924 and durvalumab is actually collected before the administration of SQ injection and start of infusion, respectively, and post-end of infusion sample for durvalumab should be collected after the infusion has actually completed. It is also equally important to record actual date and time of blood collection for PK/IK sample on the Requisition Form after drawing the sample. Sample collection for PK/IK must be from the opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, the sample collection should be from a different site.

In addition, if a patient experiences an IRR, blood samples for anti-durvalumab antibody and PK should be drawn, with no more than 15 minutes' time difference between PK and IK samples. Samples will be taken 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.

Pharmacokinetic, Pharmacodynamic, and Biomarker Sampling Schedule

Cycle	Day	PK Sampling Time for LY2510924[a]	PK Sampling Time for Durvalumab	Durvalumab Immuno-genicity	Blood for Pharmaco-genetics	Tailoring and Pharmacodynamic Biomarker			
						Plasma for Exploratory Research	Serum for Exploratory Research	Whole Blood for Immunopheno-typing Including CD34+ Counts[c] and Other Exploratory Research	Tissue for PD-L1 and Exploratory Research
—	≤7 days				X			X	
1	1	Predose[b]				X	X	X	X (Core or excisional biopsy of a tumor lesion or a recent biopsy defined by ≤3 years since last documented progression of disease)
1	1	0.5 hr +/- 15 min	10 min after end of infusion (+/-5 min)						
1	1	2 hr +/- 30 min						X	
1	1	4 hr +/- 30 min					X		
1	1	6 hr +/- 30 min							
1	1	8 hr +/- 30 min							
1	2	24-30 hr post Day 1 dose[b]					X	X	
1	15	Predose[b]					X	X	

Cycle	Day	PK Sampling Time for LY2510924[a]	PK Sampling Time for Durvalumab	Durvalumab Immuno-genicity	Blood for Pharmaco-genetics	Tailoring and Pharmacodynamic Biomarker			
						Plasma for Exploratory Research	Serum for Exploratory Research	Whole Blood for Immunopheno-typing Including CD34+ Counts[c] and Other Exploratory Research	Tissue for PD-L1 and Exploratory Research
1	15	0.5hr +/- 15 min							
1	15	2 hr +/- 30 min						X	
1	15	4 hr +/- 30 min					X		
1	15	6 hr +/- 30 min							
1	15	8 hr+/- 30 min							
1	16	24-30 hr post Day 15 dose[b]					X	X	
2	1	Predose[b]	Predose (before start of infusion)	X		X	X	X	X (On-treatment sample (Cycle 2 Day 7 ±7 days): mandatory for ovarian expansion arm (Phase 1b), optional in Phase 1a and pancreatic expansion arm in Phase 1b)
2	1	0.5 hr +/- 15 min							
2	1	4 hr +/- 30 min					X		
3	1	Predose[b]	Predose (before start			X	X	X	

Cycle	Day	PK Sampling Time for LY2510924[a]	PK Sampling Time for Durvalumab	Durvalumab Immuno-genicity	Blood for Pharmaco-genetics	Tailoring and Pharmacodynamic Biomarker			
						Plasma for Exploratory Research	Serum for Exploratory Research	Whole Blood for Immunopheno-typing Including CD34+ Counts[c] and Other Exploratory Research	Tissue for PD-L1 and Exploratory Research
			of infusion)						
4	1	Predose[b]	Predose (before start of infusion)	X			X	X	
4	1	0.5-4 hr	10 min after end of infusion (+/-5 min)						
6	1	Predose[b]	Predose (before start of infusion)						
30 days post t/ment						X	X		
90 days post-t/ment			Anytime	X					

Abbreviations: EDTA = ethylenediaminetetraacetic; hr = hour; min = minute; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic; t/ment = treatment.

[a] Samples of approximately 5 mL of whole blood will be drawn into EDTA tubes for measurement of LY2510924 in plasma.

[b] Patients should be instructed ahead of time that LY2510924 should be taken at the clinic.

[c] Includes CD34+ counts, absolute neutrophil count (ANC), absolute lymphocyte count (ALC).

Attachment 5. Protocol CXAD Data Sharing and Sample Testing Schedule

Data Sharing and Sample Testing Schedule

Study Procedures	Shared between the Two Parties	Not Shared	Timing to provide item (data/sample, etc.)	Party to Analyze Data/Sample
Clinical/oncologic history	X		Early Results Memo	Lilly
Vital signs/weight	X		Early Results Memo	Lilly
Physical examinations	X		Early Results Memo	Lilly
ECOG Performance Status	X		Early Results Memo	Lilly
12-Lead ECG 7	X		Early Results Memo	Lilly
Laboratory tests	X		Early Results Memo	Lilly
Pregnancy test – urine or serum β-HCG	X		Early Results Memo	Lilly
Other baseline physiological assessments	X		Early Results Memo	Lilly
Tumor Imaging -- assessment to support all efficacy analyses (to ensure compliance with SDTM 3.1.3)	X		Early Results Memo	Lilly
If collected, all radiologist reports — including tumor measurements and assessment of response and progression	X		Early Results Memo	Lilly
Adverse events; all safety data	X		Early Results Memo	Lilly
Tumor and Blood Biomarker Assay(s) for exploratory analysis	X		As soon as data is available during final analysis	Lilly
Tumor PD-L1 Biomarker Assay: scoring (including both dose finding cohorts and expansion arms)	X		As soon as possible but no longer than 14 calendar days of the sample receipt	Partner
Tumor PD-L1 Methods and Validation		X[a]	Within 1 month from the date the Tumor PDL-1 Biomarker Assay becomes available in the marketplace	Partner
Durvalumab Immunogenicity (ADA) Data: results	X		As soon as data is available during planned interim and/or final analysis	Partner

Study Procedures	Shared between the Two Parties	Not Shared	Timing to provide item (data/sample, etc.)	Party to Analyze Data/Sample
Durvalumab Immunogenicity (ADA) Data: methods and validation		X[a]	N/A	Partner
Durvalumab PK: results (plasma/serum concentration and PK parameters)	X		As soon as data is available during planned interim and/or final analysis	Partner
Durvalumab PK: methods and validation		X[a]	N/A	Partner
LY2510924 PK: results (plasma/serum concentration and PK parameters)	X		As soon as data is available during planned interim and/or final analysis	Lilly
LY2510924 PK: methods and validation		X[a]	N/A	Lilly

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; N/A = not applicable; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic; SDTM = Study Data Tabulation Model.

[a] In the event that the Regulatory Authorities require this information to be submitted along with the submission for Regulatory Approval for the use of the Lilly Compound in the Combination, Partner will provide this information directly to the Regulatory Authorities only for such purpose.

Attachment 6. Protocol CXAD Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report a 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 & 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 7. Protocol CXAD ECOG Performance Status

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 8. Protocol CXAD Creatinine Clearance Formula

Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

Source: Cockcroft and Gault 1976.

Attachment 9. Protocol CXAD Bayesian Model-Based, Toxicity-Band Method for Phase 1a Dose Escalation

The need to minimize the number of patients treated below the biological active dose and the understanding of LY2510924 from earlier nonclinical and clinical studies supports a more efficient dose-escalation design for Study CXAD. Therefore, the Bayesian model-based method is used in this trial to determine the next dose level, based on the predicted probabilities of dose-limiting toxicity (DLT) rates. The exact dose-escalation increment will be determined by the investigators in consultation with collaborator and Lilly CRP or designee and may be different from the model recommendation. This section introduces the background of a model-based dose-escalation method and toxicity-band design (Neuenschwander et al. 2008) and describes the key elements for this trial. Simulation results from the toxicity-band design are presented. These results are also compared with that from the simulation of traditional 3+3 design to demonstrate the benefit of implementing a toxicity-band design in this trial. Fixed and Adaptive Clinical Trial Simulator (FACTS) software version 3.5 is used for all the simulations.

Introduction of CRM-Type Approaches

The Continual Reassessment Method (hereafter, CRM; O'Quigley et al. 1990) is the first Bayesian model-based approach developed for dose-escalation studies. Compared to the traditional 3+3 design that only used current dose level DLT data to estimate the maximum tolerated dose (MTD), CRM utilizes prior dose-toxicity information and all available DLT data to effectively estimate the MTD. To improve the operating characteristics of CRM, Goodman et al. (1995), among others, have proposed modified-CRM (MCRM) procedures to make the model-based designs more acceptable in practice. The major modifications include:

- Always start at the lowest dose level.
- Limit the escalation increment.
- Escalate by cohorts rather than single patients.

Babb et al. (1998) proposed the Escalation with Overdose Control (EWOC) method that directly controls the probability of overdosing during dose escalation. EWOC is also a CRM-type method. During the escalation, EWOC selects the next dose such that the predicted probability that the new dose exceeds the MTD is equal to a prespecified feasibility bound α=0.25. The connection between CRM and EWOC is that CRM typically uses the middle (mean or median) of the MTD's posterior distribution as the next recommended dose, whereas EWOC uses the 25th percentile. Therefore, EWOC is a more conservative method than the original CRM method.

Toxicity-Band Design

Neuenschwander et al. (2008) extended the concept of EWOC (Babb et al. 1998) and proposed considering the uncertainty of the posterior distributions and using interval estimates to make the dose recommendation, herein referred to as the toxicity-band design.

The Model

A two-parameter logistic model is used to model the relationship between dose and probability of a DLT:

$$\text{logit}\{.\ (d)\} = \alpha + \beta \log\left(\frac{d}{d^*}\right), \quad \beta > 0. \ (1.1)$$

In the model, d is the true dose and $p(d)$ is the probability of a DLT at dose d. d^* is the reference dose such that α is interpreted as the log-odds of a DLT at d^*.

Toxicity Band

The probability of a DLT is categorized to 4 bands:

- Underdosing: $p(d)$ in (0, 0.20]
- Targeted toxicity: $p(d)$ in (0.20, 0.33]
- Excessive toxicity: $p(d)$ in (0.33, 0.60]
- Unacceptable toxicity: $p(d)$ in (0.60, 1.00]

Overdosing is defined as $p(d) > 0.33$.

Dose Recommendation

During the escalation, after each cohort of patients, we

1. Calculate the posterior probabilities of the 4 toxicity bands, for each dose.
2. Exclude the doses such that the posterior probabilities of overdosing are larger than 0.25 (overdosing control criteria). The remaining doses are the ones that satisfy the overdose control criteria.
3. Among the remaining doses, the dose with the highest posterior probability in the targeted toxicity band will be the model recommendation of the next dose.

The data will be evaluated on an ongoing basis until the MTD is determined. Once the MTD has been identified, a discussion between the sponsor and investigators may occur in order to treat additional patients at intermediate doses below the MTD.

Dose Range and Reference Dose

Assuming that the starting dose level is 20 mg, based on the preclinical data, the highest dose level that will be explored in this study is 40 mg and the reference dose in model (1.1) is chosen as $d^* = 40$ mg.

The Prior Distribution on Model Parameters

A Quantile-based uninformative prior (Neuenschwander et al. 2008) is used to derive a bivariate--normal prior on (α, logβ). Based on preclinical experience of LY2510924, the prior median probability of DLT for the dose levels was determined as in Table App.1. Any intermediate dose level within the starting doses to 40 mg can be explored.

Table App.1. Prior Median Probability of Dose Limiting Toxicity at Each Dose Level

Dose (mg)	Median Probability of Dose Limiting Toxicity
10	0.06
20	0.12
30	0.18
40	0.26

For each dose, the minimally informative unimode Beta distribution (a,b) is derived as the prior distribution for the probability of DLT, so that the operating characteristics of the model are robust to the selected prior distribution of DLT:

- For median probability of DLT <0.5, b=1 and a(<1) are tuned to match the median.
- For median probability of DLT >0.5, a=1 and b(<1) are tuned to match the median.

Figure App.1 shows the median and the 95% confidence interval (CI) of the prior distribution of the DLT rate at each dose level.

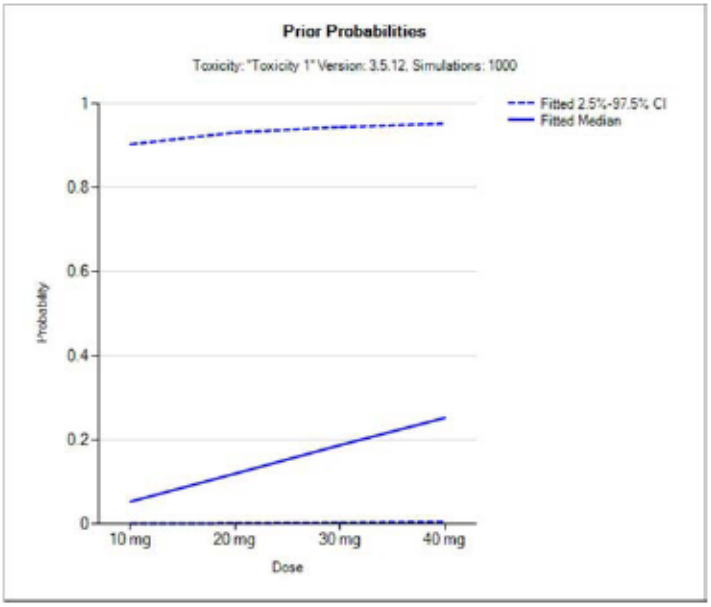

Figure App.1. The prior distribution of the dose limiting toxicity rate at each dose level.

A bivariate normal distribution was derived on (α, logβ) that stochastically gives the best fit to the 2.5%, 50%, and 97.5% quantiles of the prior probability of DLT at each dose. The parameters (α, logβ) have a bivariate normal distribution with mean=(-1.09,0.26), standard deviation=(2.17,0.51), and ρ=-0.89.

Simulation Studies

We performed simulations under different scenarios of possible dose-toxicity relationships to investigate the operational characteristics of the toxicity band versus traditional 3+3 design:

- 3-patient cohorts starting from 20 mg.
- Maximum number of patients: 15 for toxicity-band method, and 15 for traditional 3+3 method.
- Rules for stopping early for toxicity-band method: at least 6 patients have been treated at or near MTD or the probability of dose being in target band greater than 0.5 or at least 9 patients have been accrued.

Four scenarios were considered to represent a wide range of possible dose-toxicity relationships as shown in Figure App.2 and Table App.2. DLT rates for the starting dose level are chosen to take into account single patient cohorts before the true DLT rate of the MTD is set at 20~33% across scenarios. Scenarios 1, 2 and 3 have MTD at 40 mg, and Scenario 4 has the MTD at 30 mg. When the dose-toxicity curve is steep around MTD, the concern is the risk of overdosing; when the dose-toxicity curve is flat around MTD, the concern is underdosing. The simulation studies will access the performance of the toxicity-band method and compare it to the traditional 3+3 focusing on these concerns.

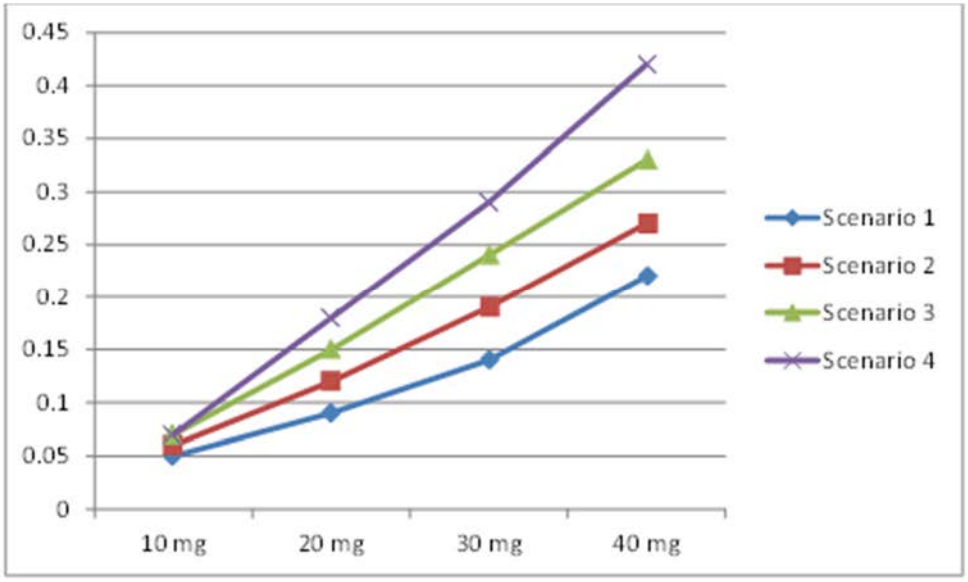

Figure App.2. The dose-toxicity relationships under each scenario.

Table App.2. The Dose-Toxicity Relationships

Dose (mg)	Scenarios			
	1	2	3	4
10	0.05	0.06	0.07	0.07
20	0.09	0.12	0.15	0.18
30	0.14	0.19	0.24	0.29
40	0.22	0.27	0.33	0.42

1000 simulations were conducted under each scenario to investigate the operational characteristics of toxicity-band and traditional 3+3 methods. The results are summarized in Table App.3.

Table App.3. Comparison of Toxicity-Band and Traditional 3+3 Method

	Scenario 1		Scenario 2		Scenario 3		Scenario 4	
Rate of Selected as MTD for Each Dose (mg/kg)	**TB**	**3+3**	**TB**	**3+3**	**TB**	**3+3**	**TB**	**3+3**
10 mg +durvalumab	**0.064**	**0.087**	**0.121**	**0.14**	**0.196**	**0.175**	**0.253**	**0.24**
20 mg + durvalumab	**0.083**	**0.157**	**0.139**	**0.219**	**0.21**	**0.315**	**0.276**	**0.371**
30 mg + durvalumab	**0.164**	**0.227**	**0.194**	**0.276**	**0.22**	**0.265**	**0.249**	**0.262**
40 mg + durvalumab	**0.689**	**0.529**	**0.546**	**0.365**	**0.374**	**0.245**	**0.222**	**0.127**
Rate of selecting Ph2 Dose below true MTD	**0.311**	**0.471**	**0.454**	**0.635**	**0.626**	**0.755**	**0.529**	**0.611**
Rate of selecting Ph2 Dose above true MTD	--	--	--	--	--	--	**0.222**	**0.127**
Rate of DLT events during the trial	**0.164**	**0.165**	**0.199**	**0.211**	**0.240**	**0.259**	**0.270**	**0.302**
Mean # Patients	**14.5**	**10.4**	**14.1**	**10.1**	**13.6**	**9.6**	**13.2**	**9.0**
Mean # Patients at true MTD	**4.7**	**3.1**	**3.7**	**2.7**	**3.1**	**2.2**	**3.4**	**3.2**

Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose; Ph2 = Phase 2.

The traditional 3+3 design is generally conservative and has a higher rate of selecting a dose level below the true MTD to be recommended for future Phase 2 studies, increasing the risk of underdosing and failure rate of Phase 2 studies. The toxicity-band method is slightly more aggressive in general and has a lower rate of MTD selection below the true level, and a higher rate of MTD selection at the true level. The mean percentages of a DLT event in each scenario are in general higher in 3+3 method, but strictly kept below the prespecified overdosing control criterion at 0.25.

Examples

Examples from Scenario 1 and Scenario 4 are provided here to illustrate how the toxicity-band method operates under certain circumstances.

Example 1

Scenario 2 has a true MTD at 40 mg with a DLT rate of 0.27 in Table App.2. With a slowly increasing relationship between the dose level and the DLT rate, patients could be assigned to dose levels under MTD and cause underdosing when DLT occurs in the first few cohorts.

With the toxicity-band method, the next recommended dose level is 40 mg after the 12th patient is treated (Figure App.3), although 2 DLTs are observed at 40 mg, and 40 mg will be declared as MTD after the 15th patient. The toxicity-band method is able to allocate more patients at the MTD dose level.

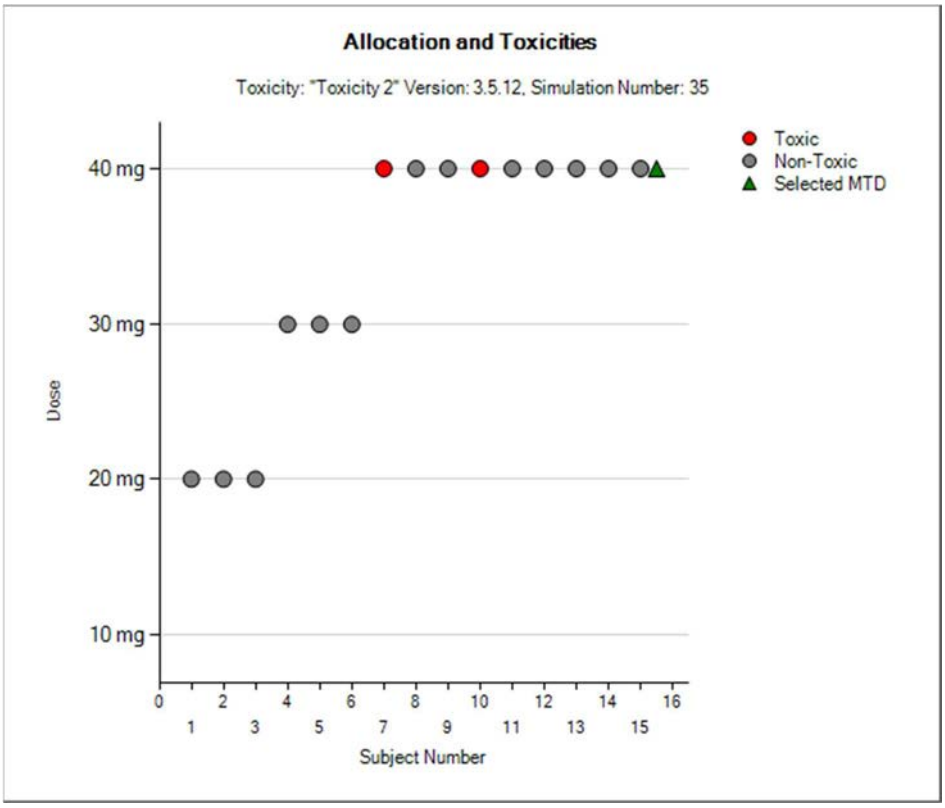

Figure App.3. A case study for Scenario 2.

Example 2

Scenario 4 has a true MTD at 30 mg with a DLT rate of 0.29 in Table App.2. With a relatively steep increasing relationship between the dose level and the DLT rate, patients could be assigned to dose levels under MTD and cause underdosing when DLT occurs in the first few cohorts.

With the toxicity-band method, the next recommended dose level is still 30 mg after the 9th patient is treated (Figure App.4), although 2 DLTs are observed at 30 mg, and 30 mg will be declared as MTD after the 15th patient, even though there are 3 DLTs observed. The toxicity-band method has also allocated more patients at the MTD dose level.

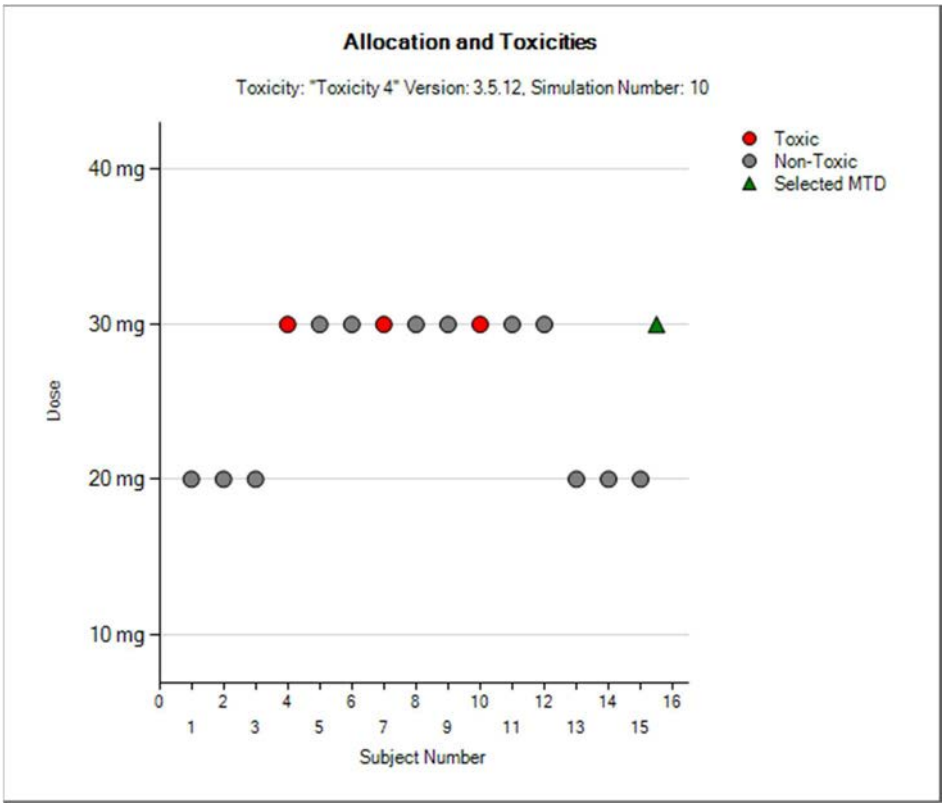

Figure App.4. A case study for Scenario 4.

Summary

As a conclusion, based on the simulation studies on a variety of scenarios and the illustrative examples, the toxicity-band method is slightly more aggressive than the traditional 3+3 design, and therefore provides a lower underdosing rate and a higher MTD selection rate, with a well-controlled overdosing rate at a prespecified criterion. Therefore, the modified 3+3 method that incorporates the principles of the toxicity-band method will be used in this study rather than the traditional 3+3 escalation paradigm.

Attachment 10. Protocol CXAD RECIST Version 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumours (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (slice thickness ≤5 mm)
- 10-mm calliper measurement by clinical examination (nonmeasurable lesions if cannot be accurately measured with callipers)
- 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10-mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone Lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are nonmeasurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Nontarget Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Nonnodal target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be able to be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the CRF in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or callipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are able to be assessed by clinical examination.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10-mm diameter as assessed using callipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-Ray: Chest CT is preferred over chest x-ray when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator-dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in CR. Specific guidelines for both prostate-specific antigen response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a

potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

PET Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a CR or PR in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

PR: At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

SD: Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response (CR): Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological or normal in size (<10-mm short axis).

Non-CR/Non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The best overall response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is conducted/made at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table App.4 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table App.4. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Table App.5 is to be used when patients have *nonmeasurable* disease only.

Table App.5. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; NE = not evaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6 to 8 weeks is reasonable. Normally, all target and nontarget sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontarget lesions is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 11. Protocol CXAD Durvalumab Monotherapy Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions

Pneumonitis

AEs of pneumonitis are of interest as pneumonitis has been reported with anti-PD-1 mAbs (Topalian et al. 2012). Initial work-up should include 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 the table below.

Infusion-Related Reactions

All infusion-related reactions occurring from the start of durvalumab infusion up to 48 hours after the infusion start time are considered AESIs. All infusion reactions are to be considered SAEs and should be reported as per the SAE reporting guidelines described in Section 8.1.2.6.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related AEs during the conduct of this study. Potential immune-related AEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Patients should be monitored for signs and symptoms of immune-related AEs. In the absence of an alternative etiology (eg, infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

All AEs of possible infusion reactions are to be reported as IRRs, if occurring from the start of durvalumab infusion up to 48 hours after the infusion start time.

Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions 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 (immunoglobulin E-mediated) and anaphylactoid reactions against the mAb, 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 infusion-related reactions are outlined in the table below.

Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al. 2012). Inflammatory hepatitis has been reported in 3% to 9% of patients treated with anti-CTLA-4 monoclonal antibodies (eg, ipilimumab). The clinical manifestations of ipilimumab-treated patients included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3x ULN and concurrent increase in total bilirubin to be greater than 2x 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 (eg, 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 the table below.

Cases where a patient shows an AST or ALT ≥3x ULN or total bilirubin ≥2xULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

Criteria for Hy's Law (FDA 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
- Among study patients showing such aminotransferase elevations, often with aminotransferases much >3x ULN, one or more also show elevation of serum total bilirubin to >2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Hepatic function abnormality

Hepatic function abnormality in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor, unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by Lilly and collaborator.

Cardiovascular Disorders

For all cardiovascular AEs, CTCAE Grades 1 to 4, the investigator should consider consultation with a cardiologist experienced in the management of the specific AE being evaluated.

Gastrointestinal Disorders

Diarrhea/colitis is the most commonly observed treatment-emergent SAE when durvalumab 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 durvalumab are provided in the table below.

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 the table below.

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 the table below.

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 the table below.

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 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).

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 the table below.

MEDI4736 Monotherapy Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion Related, and Non Immune-Mediated Reactions - 19 August 2016 Version

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 **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 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: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	It is recommended that management of irAEs follows the guidelines presented in this table: − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). − In the absence of a clear alternative etiology, all events should be considered potentially immune related. − 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. − 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 for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. − 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.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE Immune-related 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/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 methylprednisone 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 treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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. – 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 patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (stool frequency of <4 over baseline per day)	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 (stool frequency of 4 to 6 over baseline per day)	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 weeksa. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consult 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 treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**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. – 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-PCP 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 > to 3 × ULN and/or TB > to 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 5 × ULN and/or TB >1.5 to 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	**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, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		regimen after completion of steroid taper.	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 (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 treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × 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 elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study	**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 (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 treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		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.	
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	Hold study drug/study regimen until resolution to Grade ≤1 or baseline.	**For Grade 2:** − Consider symptomatic treatment, including hydration,

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	to 3.0 × baseline; >1.5 to 3.0 × ULN)	• 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.	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-PCP 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 treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
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 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	**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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**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:** – Consult endocrinologist. – 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, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – 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. – 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.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically	**For Grade 2 (including those with symptomatic endocrinopathy):** – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		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 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.	corticosteroids. – Initiate hormone replacement as needed for management. – Evaluate endocrine function, and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, 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, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP 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, 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.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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 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:** – Discuss 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 irAE does not resolve to Grade ≤1 within 30 days.	**For Grade 3 or 4:** – Discuss with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			2 mg/kg/day or equivalent. **For Grade 4:** Permanently discontinue study drug/study regimen. − 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 with the study physician.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– 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 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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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 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 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.

[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.

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; ILD Interstitial lung disease; irAE Immune-related 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 ; 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).

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.	Treat accordingly, as per institutional standard.
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.	Treat accordingly, as per institutional standard.
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."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Attachment 12. Protocol CXAD Echocardiographic Guidelines

Echocardiography (ECHO)

In this study, ECHO images will be acquired to screen patients for eligibility to enter the study, ie, baseline normal cardiac structure and function, normal pulmonary artery pressure, and absence of significant valvular disease (defined herein as no valvular regurgitation except for mild tricuspid, mild mitral, or mild aortic regurgitation, and no more than mild mitral or aortic valvular stenosis). ECHO should also be performed if clinically indicated in the opinion of the investigator to manage any cardiovascular or cardiopulmonary AEs. Determination of normalcy status requires objective evaluation of cardiac chamber size and function and attention to the use of appropriate techniques in the performance of the ECHO examinations, in particular the use of standardized settings during the acquisitions of color flow Doppler imaging. Therefore, because quantitative ECHO is the goal, stringent criteria for image quality and reproducibility are essential.

In addition to qualitative assessment of valvular regurgitation when or if detected (trace, mild, moderate, or severe according to Singh et al. 1999 and Zoghbi et al. 2003) and qualitative/quantitative assessment of valvular stenosis when or if detected (mild, moderate, or severe, using mean and peak pressure gradient in mm Hg and orifice area in cm^2 as applicable), other ECHO parameters to be serially quantified are LV cavity size (diameters, volumes), LVEF, LV mass and mass index, diastolic function based on mitral flow velocity, mitral deceleration time, pulmonary venous flow pattern, tissue Doppler, extrapolation of LV end-diastolic pressure by E/Em, left atrial volume index, and extrapolation of pulmonary artery systolic pressure when obtainable.

An ECHO with no clinically significant abnormalities is one defined specifically as one in which the LV (Schiller et al. 1989) internal dimension in diastole should be ≤ 2.8 cm/m^2, the left atrial (Tsang et al. 2002) end-systolic volume should be ≤ 36 mL/m^2, the LVEF (Oh et al. 2006) should be $\geq 50\%$ without regional wall motion abnormalities, 2-dimensional ECHO-derived LV mass index should be ≤ 115 g/m^2 for males and ≤ 99 g/m^2 for females, the pulmonary artery pressure should be normal (tricuspid regurgitation jet velocity ≤ 2.5 m/s and/or pulmonary valve flow acceleration time ≥ 120 ms), the LV diastolic function (Khouri et al. 2004) should be normal (screening: mitral deceleration time ≥ 150 ms and ≤ 250 ms, mitral E/A ratio ≥ 0.75 and ≤ 1.5, mitral E velocity divided by Doppler mitral annular velocity [E/Em] <15), and no evidence for pericardial or congenital heart disease. In addition, there should be no evidence for more than mild mitral or aortic stenosis (mitral valve area should be >2.0 cm^2, and aortic valve area should be >1.5 cm^2) and no evidence of more than mild mitral or aortic regurgitation (Singh et al. 1999; Zoghbi et al. 2003). Patients enrolled in the study may have evidence for tricuspid (trace or mild), pulmonary, mitral (trace or mild), or aortic (trace or mild) regurgitation by Doppler techniques (Singh et al. 1999; Zoghbi et al. 2003).

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Appendix: Qualitative and Quantitative Parameters for Grading Valvular (Mitral and Aortic) Regurgitation Severity

Please refer to references below for information on qualitative and quantitative parameters for grading valvular (mitral and aortic) regurgitation severity.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, Lehman B, Benjamin EJ. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol.* 1999;83(6):897-902.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Craft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16(7):777-802.

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Attachment 13. Protocol CXAD Protocol Amendment I2V-MC-CXAD(b) Summary A Phase 1a/1b Study of CXCR4 Peptide Antagonist (LY2510924) Administered in Combination with the Anti-PD-L1 Antibody, Durvalumab (MEDI4736), in Advanced Refractory Solid Tumors

Overview

Protocol I2V-MC-CXAD A Phase 1a/1b Study of CXCR4 Peptide Antagonist (LY2510924) Administered in Combination with the Anti–PD-L1 Antibody, Durvalumab (MEDI4736), in Advanced Refractory Solid Tumors has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The I2V-MC-CXAD protocol (a) was amended to make the following changes:

- Section 5.5.2.4: Clinical safety information on durvalumab updated.
- Section 6.1.3: Exclusion Criterion [16] expanded to include previous participation in any randomized controlled trial that included arms with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3, rather than only either durvalumab or tremelimumab.
- Synopsis and Section 6.2: Clarified that patients will be allowed to continue until they fulfill 1 or more of the study discontinuation criteria.
- Sections 6.2 and 8.3.1.2: Clarified that patients will not be permitted to continue study therapy if progression occurs after confirmed response.
- Section 7.2.2.1: Added or modified existing DLT criteria to:
    - ≥Grade 3 leukocytosis (leukocytes >100,000/μL) of any duration, or leukocytosis/granulocytosis causing clinical symptoms
    - Any Grade 4 non-laboratory AE
    - Any Grade 3 laboratory value, and modified stipulations that the abnormal value must be associated with clinically significant symptoms and persist for >7 days
    - Any Grade 4 laboratory abnormalities
- Section 7.2.2.2: For Phase 1a, any DLT-equivalent toxicities observed in Cycle 2 and beyond will also be considered in dose escalation and determining MTD/recommended Phase 2 dose. Additionally, if the DLT observation period is extended to Cycle 2, patients discontinuing in Cycle 2 in the absence of DLT-equivalent toxicity will be evaluable for DLT assessments.

- Section 7.2.4: Wording added that for Phase 1a and 1b, the DLT observation period will be extended to Cycle 2 if a DLT-equivalent toxicity is observed during Cycle 2 in any cohort in Phase 1a.
- Table CXAD.7.2: Dose adjustment of LY2510924 to align with newly added DLT criterion for leukocytosis.
- Section 8.1.3.1: Typographical error was corrected.
- Section 8.3.1.2: Patients with a decline in Eastern Cooperative Oncology Group (ECOG) performance status >1 will not be permitted to continue study treatment after confirmed progression of disease.
- Section 10.10: Wording added that if the DLT-observation period is extended to 2 cycles during Phase 1a, analysis will include DLT-equivalent toxicities occurring in Cycle 2.
- Attachment 1 and Attachment 4: Correction: For Serum, Plasma, and Whole Blood Samples for Biomarkers, baseline whole blood samples must be collected ≤7 days prior to Cycle 1 Day 1.
- Attachment 4: Correction: immunogenicity samples will be collected 90 days post durvalumab treatment.
- Attachment 11: Durvalumab dose modification guidelines have been updated.

A detailed list of changes made in this amendment is below. Some minor editorial changes may not be listed.

Revised Protocol Sections

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

2. Synopsis

...

Planned Duration of Treatment: ~~6 months or~~ Patients will receive study therapy until the patient fulfills 1~~one~~ of the criteria for study discontinuation. Patients ~~demonstrating a benefit from treatment~~ may continue on combination therapy beyond initial radiological disease progression in the absence of clinically significant deterioration. ~~6 months if the patient and investigator feel that the patient is benefiting from treatment~~. If a patient experiences an adverse event (AE) that requires the patient be discontinued from durvalumab or LY2510924, the patient should be discontinued from both study drugs.

...

5.2. Rationale for Protocol Amendment (a)

…

~~Attachment 13 contains a detailed list of changes made in this amendment. Some minor editorial changes may not be listed.~~

5.3. Rationale for Protocol Amendment (b)

The I2V-MC-CXAD protocol (a) was amended to make the following changes:

- Section 5.5.2.4: Clinical safety information on durvalumab updated.
- Section 6.1.3: Exclusion Criterion [16] expanded to include previous participation in any randomized controlled trial that included arms with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3, rather than only either durvalumab or tremelimumab.
- Synopsis and Section 6.2: Clarified that patients will be allowed to continue until they fulfill 1 or more of the study discontinuation criteria.
- Sections 6.2 and 8.3.1.2: Clarified that patients will not be permitted to continue study therapy if progression occurs after confirmed response.
- Section 7.2.2.1: Added or modified existing DLT criteria to:
  - ≥Grade 3 leukocytosis (leukocytes >100,000/μL) of any duration, or leukocytosis/granulocytosis causing clinical symptoms
  - Any Grade 4 non-laboratory AE
  - Any Grade 3 laboratory value, and modified stipulations that the abnormal value must be associated with clinically significant symptoms and persist for >7 days
  - Any Grade 4 laboratory abnormalities
- Section 7.2.2.2: For Phase 1a, any DLT-equivalent toxicities observed in Cycle 2 and beyond will also be considered in dose escalation and determining MTD/recommended

Phase 2 dose. Additionally, if the DLT observation period is extended to Cycle 2, patients discontinuing in Cycle 2 in the absence of DLT-equivalent toxicity will be evaluable for DLT assessments.

- Section 7.2.4: Wording added that for Phase 1a and 1b, the DLT-observation period will be extended to Cycle 2 if a DLT-equivalent toxicity is observed during Cycle 2 in any cohort in Phase 1a.
- Table CXAD.7.2: Dose adjustment of LY2510924 to align with newly added DLT criterion for leukocytosis.
- Section 8.1.3.1: Typographical error was corrected.
- Section 8.3.1.2: Patients with a decline in Eastern Cooperative Oncology Group (ECOG) performance status >1 will not be permitted to continue study treatment after confirmed progression of disease.
- Section 10.10: Wording added that if the DLT-observation period is extended to 2 cycles during Phase 1a, analysis will include DLT-equivalent toxicities occurring in Cycle 2.
- Attachment 1 and Attachment 4: Correction: For serum, plasma, and whole blood samples for biomarkers, baseline whole blood samples must be collected ≤7 days prior to Cycle 1 Day 1.
- Attachment 4: Correction: immunogenicity samples will be collected 90 days post durvalumab treatment.
- Attachment 11: Durvalumab dose modification guidelines have been updated.

Attachment 13 contains a detailed list of changes made in this amendment. Some minor editorial changes may not be listed.

[Note: With the addition of new Section 5.3 (above), subsequent heading numbers increased by the appropriate level through the end of Section 5: eg, 5.3 Objectives, now 5.4 Objectives.]

5.5.2. Durvalumab

…

5.5.2.4. Summary of Clinical Experience

…

Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. Potential risks are events with a potential inflammatory mechanism which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. These risks include gastrointestinal AEs such as colitis and diarrhea, pneumonitis, nephritis and acute renal failure; hepatic AEs such as hepatitis and liver enzyme elevations and dermatitis; and

endocrinopathies such as hypo- and hyper-thyroidism, hypophysitis, and adrenal insufficiency. Additional treatment-emergent immune-related events, including pancreatitis, neuropathy, and neuromuscular toxicity, have been reported with checkpoint inhibitor treatment. ~~Immune-related AEs, which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy.~~ These events are manageable by available/established treatment guidelines as described in the study protocol.

Adverse Event Profile of Durvalumab Monotherapy

~~Study CD-ON-MEDI4736-1108: The safety profile of durvalumab monotherapy in the 694 patients with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108 has been broadly consistent with that of the overall 1279 patients who have received durvalumab monotherapy (not including patients treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07 May 2015, among the 694 patients treated with durvalumab 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, a total of 378 patients (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥5% of patients) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥Grade 3 events occurring in 65 patients (9.4%). Treatment-related ≥Grade 3 events reported in 3 or more patients (≥0.4%) were fatigue (12 patients, 1.7%); increased AST (7 patients, 1.0%); increased gamma-glutamyltransferase (GGT; 6 patients, 0.9%); increased ALT (5 patients, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 patients, 0.4% each). Six patients had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 patient had a treatment-related Grade 5 event (pneumonia). Treatment-related SAEs that occurred in ≥2 patients were colitis and pneumonitis (3 patients each). A majority of the treatment-related SAEs were ≥Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 patients (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 patients). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥Grade 3 in severity and resolved with or without sequelae.~~

~~Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-MEDI4736-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W.~~Identified risks with durvalumab are diarrhea, increases in transaminases, pneumonitis, and colitis.

Potential risks include endocrinopathies (hypo- and hyper-thyroidism, hypophysitis, and adrenal insufficiency), hepatitis/hepatotoxicity, neurotoxicities, nephritis, pancreatitis, dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, and immune complex disease. Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies, AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 3.5% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines in Attachment 11).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

6.1.3. **Exclusion** Criteria

…

[16] Previous participation in any randomized controlled trial that included arms with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-cytotoxic T lymphocyte-associated antigen-4 antibody (including but not limited to ipilimumab, durvalumab, or tremelimumab) or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways such as CD137, GITR, TIM-3, and LAG3~~.either durvalumab or tremelimumab~~, irrespective of actual treatment received on the trial.

…

6.2. **Summary of Study Design**

…

Treatment decisions related to patient management and whether to treat a patient with advanced refractory solid tumors with additional cycles of study therapy will be based on RECIST v1.1. ~~Rare exceptions for c~~Continuation with 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 protocol therapy and both the investigator and sponsor, in consultation with collaborator (AstraZeneca, London, United Kingdom), agree that continuing protocol therapy is in the patient's best interest. Patients will not be permitted to continue study therapy if progression occurs after confirmed response (complete response [CR] or partial response [PR] as defined by RECIST v1.1) in the target lesions (regardless of the appearance of new lesions), ie,

the response and progression events both occurred in the target lesions while receiving study therapy.

At the sponsor's discretion, scans and measurements may be collected and reviewed by independent radiologists using RECIST v1.1 at a later date, or at any time during the study.

Study treatment will continue ~~The planned duration of treatment is 6 months or~~ until the patient fulfills 1 of the criteria for study discontinuation (Section 6.3). Patients ~~demonstrating a benefit from treatment~~ may continue on combination therapy beyond initial radiological disease progression ~~6 months if the patient and investigator feel that the patient is benefiting from treatment~~ in the absence of clinically significant deterioration (Section 8.3.1.2). If a patient experiences an AE that requires the patient be discontinued from durvalumab or LY2510924, the patient should be discontinued from both study drugs (Section 7.2.5).

…

6.3.2. Discontinuation of Patients from Study or Study Drug

…

In addition, patients will be discontinued from the study drugs and/or from the study in the following circumstances:

…

- The patient has confirmed evidence of progressive disease by RECIST v1.1. In the setting of disease progression, the patient will discontinue from study drug(s); however, the patient will continue to be followed on study. In the setting of unconfirmed/equivocal progression, the patient should remain on study treatment until the next assessment period or up to 12 weeks after consultation with a Lilly physician. See Section 8.3.2.1 for additional details. ~~Rare exceptions for continuation with 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 protocol therapy and both the investigator and sponsor, in consultation with the collaborator, agree that continuing protocol therapy is in the patient's best interest.~~
- …

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

A DLT is defined as 1 of the following AEs reported during the Phase 1a DLT observation period, if considered to be definitely, probably, or possibly related to either study regimen by the investigator; and fulfills any 1 of the following criterion using National Cancer Institute (NCI) CTCAE version (v) 4.03:

1. Non-laboratory abnormalities (clinical~~Nonhematologic~~ toxicity):

   ~~a. Nonlaboratory:~~

   ai. Any Grade 4 immune-related AE (Attachment 10)
   b. Any Grade 4 non-laboratory AE
   cii. Any CTCAE Grade ≥3 QT prolongation AE
   diii. …
   gvi. ≥Grade 3 toxicity lasting an extended period of time despite optimal supportive care (for example, nausea, vomiting, and diarrhea lasting >3 days; fatigue lasting >7 days)

2b. Laboratory abnormalities:
   ai. Any Grade 3 ~~or Grade 4~~ laboratory value if:
      i1. Medical intervention is required to treat the patient, or
      ii. Associated with clinically significant symptoms. Examples include but are not limited to, ≥Grade 3 thrombocytopenia if associated with bleeding and requires platelet transfusion, ≥Grade 3 febrile neutropenia, or
      iii2. The abnormality persists for >7 ~~14~~ days (excluding amylase and lipase)
   b. Any Grade 4 laboratory abnormalities
   cii. …
   d. ANC >75,000/µL or ≥Grade 3 leukocytosis (leukocytes >100,000/µL) of any duration, or leukocytosis/granulocytosis causing clinical symptoms

~~2. Hematologic toxicity, as follows:~~

   ~~a. Grade 4 toxicity lasting >7 days, or~~
   ~~b. ≥Grade 3 thrombocytopenia if associated with bleeding and requires platelet transfusion, or~~
   ~~c. ≥Grade 3 febrile neutropenia~~
   ~~d. ANC >75,000/µL~~

3. …
5. Any other ≥Grade 3 ~~nonhematological~~ toxicity, except for the exclusions listed below.

…

7.2.2.2. Dose-Escalation Method

…

During the dose-escalation period, the investigators and Lilly CRP or designee in consultation with collaborator will consider the model recommendation, ~~and~~ the observed DLT rate, and any DLT-equivalent toxicities observed in Cycle 2 and beyond at each cohort to determine the next dose level and determine when to stop dose escalation. …

… For the purpose of making decisions on dose escalation from a safety perspective, patients will be considered evaluable (DLT-evaluable population) if they have either completed the DLT-

observation period (Cycle 1) and received the scheduled durvalumab dose and at least 75% of LY2510924 doses in Cycle 1 or ~~who~~ have discontinued study treatment or study participation before completing Cycle 1 due to a DLT. If the DLT-observation period is extended to Cycle 2, patients who discontinued during Cycle 2 in the absence of DLT-equivalent toxicity will be considered evaluable for DLT assessment.

…

7.2.4. DLT-Equivalent Toxicity

A DLT-equivalent toxicity is defined as an AE occurring during Cycle 2 and beyond in Phase 1a that would have met the criteria for a DLT if it had occurred during Cycle 1 or during any cycle in Phase 1b. The DLT-observation period will be extended to Cycle 2 if a DLT-equivalent toxicity is observed during Cycle 2 in any cohort in Phase 1a. …

7.2.5.1.1. LY2510924 Dose Adjustments and Delays

…

Table CXAD.7.2. Dose Adjustments of LY2510924

Event	Intervention	Dose Adjustment
~~Cytosis~~ Leukocytosis (ANC >75,000/µL or leukocytes >100,000/µL)	1) Interrupt LY2510924 2) Recheck WBC, ANC every 2 to 3 days until ANC decreases to <50,000/µL	Reduce 1 dose level
…		

8.1.3.1. Electrocardiograms

…

QT prolongation that meets CTCAE Grade ≥3 criteria will be considered a DLT criterion in the Phase 1a~~b~~ portion of this trial; in the other parts of the study, this should be considered grounds for early withdrawal or discontinuation based on the investigator's assessment. …

8.3.1. **RECIST** Version 1.1 with Confirmatory Scan for Disease Progression

8.3.1.1. **Rationale for RECIST** Version 1.1 with Confirmatory Scan for Disease Progression

…

8.3.1.2. **Application of RECIST** Version 1.1 with Confirmatory Scan for Disease Progression

For Study CXAD, based on the unique response to immunotherapy and guidelines from regulatory agencies (for example, the European Medicines Agency's "Guideline on the

evaluation of anticancer medicinal products in man" [EMA/CHMP/205/95/Rev.4] for immune modulating anticancer compounds), the following will be applied, in addition to standard RECIST v1.1 criteria:

- …
- For patients who continue to receive clinical benefit, and in the absence of clinically significant deterioration despite evidence of objective progressive disease with the confirmatory scan, the patient may continue study treatment at the discretion of the investigator, in consultation with the Lilly CRP or designee. Patients with a decline in ECOG performance status to >1 will not be permitted to continue study treatment after confirmed progression of disease.

NOTE: In determining whether or not progression can be confirmed, the site study team should consider all target lesions, nontarget lesions, and new lesions. Patients will not be permitted to continue study therapy if progression occurs after confirmed response (CR or PR as defined by RECIST v1.1) in the target lesions (regardless of the appearance of new lesions), ie, the response and progression events both occurred in the target lesions while receiving study therapy.

10.10. Interim Analyses

Data will be reviewed on a cohort-by-cohort basis during Phase 1a of the study, until the MTD is determined. The purpose of these cohort-by-cohort reviews is to evaluate the cumulative safety data (Cycle 1 and all later cycles) at each dose level(s) that has/have enrolled study patients, and determine if a DLT has been observed that would suggest MTD has been met or exceeded. …

In Phase 1b, if a DLT-equivalent toxicity occurs in one-third or more of patients during Cycle 1 (with a minimum of 6 patients enrolled), a data review will be performed to determine whether to continue at the current LY2510924 dose or whether the dose of LY2510924 should be reduced. If the DLT-observation period is extended to 2 cycles during Phase 1a, this analysis will also include DLT-equivalent toxicities occurring in Cycle 2.

…

Attachment 1. Protocol CXAD Study Schedule

Baseline, During and Poststudy Assessments

	Baseline		Cycle 1		Cycle 2	Cycle 3-n	Follow-Up				Comments
Relative Day Within a Cycle	**<28 days**	**<7 days**	**1**	**15**	**1**	**1**	**30 day**	**60 day**	**90 day**	**LT FU[a]**	Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient. All assessments to be performed pre-infusion unless stated otherwise.

…

								Baseline sample for whole blood only, and must be collected ≥≤7 days prior to Cycle 1 Day 1. See Attachment 4 for exact timing.
Serum, Plasma, and Whole Blood Samples for Biomarkers		x	See Attachment 4 for exact timing.	x				

Attachment 4. Protocol CXAD Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Biomarker Sampling Schedule

...

Pharmacokinetic, Pharmacodynamic, and Biomarker Sampling Schedule

						Tailoring and Pharmacodynamic Biomarker			
Cycle	**Day**	**PK Sampling Time for LY2510924[a]**	**PK Sampling Time for Durvalumab**	**Durvalumab Immuno-genicity**	**Blood for Pharmaco-genetics**	**Plasma for Exploratory Research**	**Serum for Exploratory Research**	**Whole Blood for Immunopheno-typing Including CD34+ Counts[c] and Other Exploratory Research**	**Tissue for PD-L1 and Exploratory Research**
—	~~<~~≤7 days				X			X	
…									
90 days post-t/ment			Anytime	X	~~X~~				

Attachment 11. Protocol CXAD Durvalumab Monotherapy Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion Related, and Non Immune–Mediated Reactions

[Note: Formatting changes made to the table are not noted below.]

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Immune-Mediated Reactions		
	Dose Modifications	**Toxicity Management**
Immune-related Adverse Events (Overall Management For toxicities not noted below)	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/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/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. Grade 1: No dose modification Grade 2: Hold study drug/study regimen dose until Ggrade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 ~~• If toxicity improves to baseline then treat at next scheduled treatment date~~ Study drug/study treatment can be resumed ~~at the next scheduled dose~~ once event stabilizes to Ggrade ≤1 ~~and 5-7 days have passed~~ 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, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	It is recommended that management of irAEs follow the guidelines presented in this table – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events – For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone 1-2mg/kg/day PO or IV equivalent – If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/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 (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient

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	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue study drug/study regimen	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen		

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	General Guidance ~~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	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult

3

	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Ggrade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, ~~baseline~~	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		then the decision to reinitiate study drug/regimen ~~at next scheduled treatment date~~ will be based upon treating physician's clinical judgment and after completion of steroid taper. ~~Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper~~	– If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days ~~4 weeks~~ and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii 1] – 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 [e.g. 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 – Hospitalize the patient – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii]

[+] ~~ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"~~

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance ~~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 (e.g., disease progression, other medications, 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)	No dose modification	For Grade 1 diarrhea : - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • ~~If~~ If toxicity improves to ≤ Grade 1, ~~baseline~~ then ~~treat at next scheduled treatment date~~ • s~~S~~tudy drug/study regimen can be resumed ~~at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed~~ after completion of steroid taper	For Grade 2 diarrhea: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., 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 3-5 days or worsens despite prednisone at 1-2 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 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[2]). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult study physician if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	For Grade 3 or 4 diarrhea: – 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 – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/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 improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[2] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade		– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1 (AST or ALT > ~~ULN~~ to 3 times ULN and/or TB > ~~ULN~~ to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times 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~~ If toxicity improves to ≤ Grade 1 or baseline, resume study drug/study regimen ~~then treat at next scheduled treatment date~~ • ~~Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed~~ after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[3] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to

[3] ~~ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" , by Michael Postow MD~~

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	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 ~~administration at the next scheduled dose~~ if elevations downgrade ≤ 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 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 >	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/dayor equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please referto current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[iv]	
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade	General Guidance	– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum 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 (e.g., 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

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper ~~treat at next scheduled treatment date~~ ~~Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 for 5-7 days have passed after completion of steroid taper~~	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. – Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	– 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 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance ~~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 modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat	For Grade 2 : – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		as Grade 3 • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper ~~administration at next scheduled dose~~ • ~~Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after~~	worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs
	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 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 improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)	General Guidance	– Consult Endocrinologist – 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, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 ~~• If toxicity improves to baseline then treat at next scheduled treatment date~~ Study drug/study regimen can be resumed ~~at the next scheduled dose~~ once event stabilizes and ~~to grade ≤1 and 5-7 days have passed~~ 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, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	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 endocrine function, and as clinically indicated, consider pituitary scan – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). - – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled ~~Resume study drug/study regimen administration if controlled at the next scheduled dose~~ Study drug/study regimen can be resumed ~~at the next scheduled dose~~ once event stabilizes ~~to grade ≤1~~ and ~~5-7 days have passed~~ after completion of steroid taper	For Grade 3 or 4: – Consult endocrinologist – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Once improving, gradually taper immunosuppressive steroids over ≥28 days ~~4 weeks and~~ consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer- related infections [Category 2B recommendation]) – Discuss with study physician
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade	General Guidance	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			conduction investigations) – Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	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. o If toxicity worsens then treat as Grade 3 or Grade 4 ~~o If toxicity improves to baseline then treat at next scheduled treatment date~~ • Study drug/study regimen can be resumed ~~at the next scheduled dose~~ once event improves ~~stabilizes~~ to Grade ≤1 and ~~5 7 days have passed~~ after completion of steroid taper	– Discuss with the study physician – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1	For Grade 3 or 4: – Discuss with study physician

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		• Permanently discontinue s~~S~~tudy drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	– Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥28 days ~~4 weeks~~
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		General Guidance ~~Any Grade~~	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which 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 (e.g., disease progression, infections, metabolic syndromes and medications, etc.). 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 (e.g., 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 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 IVIG and followed by plasmapheresis if

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			not responsive to IVIG
	Grade 1	No dose modification	– Discuss 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	Grade 2 – Discuss 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 (e.g., gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. 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 IVIG. 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 present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

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	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: – Discuss with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It 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 IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: 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 IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

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Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	– Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing,hypotension, tachycardia, etc.)
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 1 or Grade 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 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	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Non-immune Mediated Reactions (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"		
~~CTC Grade/~~Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modification	Toxicity Management
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
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 ~~at next scheduled dose~~. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in 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."

AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

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[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 NCI CTCAE version 4.03
[iii] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[iv] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

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