Investigational Drug Substance(s)	Durvalumab (MEDI4736)
Study Number	ESR-17-12765
Version Number	8
Date	23 MAY 2022

An open-label, phase II study of Durvalumab (MEDI4736) in combination with Cetuximab in previously treated/ metastatic Head and Neck Squamous Cell Carcinoma

Sponsor: Trisha Wise-Draper MD PhD (University of Cincinnati)

PROTOCOL SYNOPSIS

Clinical Protocol ESR-17-12765/UCCI-HN-17-02

Study Title: An open-label, phase II study of durvalumab (MEDI4736) in combination with cetuximab in previously treated recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
Protocol Number: ESR-17-12765
Clinical Phase: Phase II
Study Duration: The sponsor estimates that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last visit.
Investigational Product(s) and Reference Therapy: durvalumab (MEDI4736) will be supplied in glass single-dose vials containing 500 mg (10 mL) of liquid solution at a concentration of 50 mg/mL to be further diluted for intravenous (IV) administration. Cetuximab is sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Cetuximab will be supplied at a concentration of 2 mg/mL in 100 mg (50 mL) or 200 mg (100 mL), single-use glass vials.
Research Hypothesis: Addition of durvalumab to standard of care Cetuximab in recurrent/ metastatic HNSCC will result in increased response rates and the combination is tolerable.
Objectives: **Primary Objective:** 1. To determine the objective response rate of the combination of durvalumab and cetuximab using RECIST 1.1 in subjects with recurrent and/or metastatic HNSCC.

Secondary Objective(s):

1. To determine the safety and tolerability of durvalumab intravenously (IV) combined with standard of care cetuximab in patients with recurrent and/or metastatic HNSCC.
2. To determine disease control rate (DCR= CR [complete response] + PR [partial response] + SD [stable disease]) at 6 months in subjects receiving durvalumab and cetuximab with recurrent and/or metastatic disease.
3. To estimate the progression-free survival (PFS) using RECIST 1.1 in all patients receiving durvalumab and cetuximab with recurrent and/or metastatic HNSCC.
4. To estimate the overall survival (OS) separately in all patients receiving durvalumab and cetuximab with recurrent and/or metastatic HNSCC.
5. To estimate the duration of response (DOR) in all patients receiving durvalumab and cetuximab with recurrent and/or metastatic HNSCC.

Exploratory Objective(s):

1. To explore potential predictive biomarkers of efficacy, such as response, PFS and OS, in subjects receiving a combination of cetuximab and durvalumab by analyzing fresh or archival tumor specimens for proteins involved in regulating immune responses including PD-L1 and PD-L2 as well as EGFR expression.
2. Evaluate archival tumor specimens for CD4, CD8 and T reg ratios as well as Natural Killer cells (NKs) in order to determine immune composition in the tumor microenvironment and tumor. The study will also determine immune cell activity with KI-67 and granzyme expression in tumor.
3. To study peripheral blood T cell response after anti-PDL-1 treatment by multi-color flow- cytometry to determine type of peripheral immune response.

Study Design:

This study will be a single center, non-randomized, single-cohort trial of the combination of durvalumab and cetuximab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (HNSCC). We plan to enroll approximately 36 subjects in this trial to examine the safety and efficacy of combining durvalumab with cetuximab in this patient population. Enrolled patients will receive standard of care cetuximab (500 mg/m2) IV over 120 minutes on day -14 (unless the patient is already on Cetuximab, they may continue without washout and without a new baseline dose); followed on week 2 with cetuximab 500 mg/m2 IV over 60 minutes (continued every 2 weeks) combined with durvalumab (1500 mg every 4 weeks) intravenously (IV). Patients will be followed weekly during treatment for the first month, then monthly while on treatment. Radiographic imaging will be done every 8 weeks to assess response to treatment. Overall Response Rate (ORR) (RECIST v1.1) will be used as the primary efficacy end-point. Patients will be monitored for adverse events, which will be graded in severity using the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. This regimen will be continued until progression of disease or development of intolerable side effects, intercurrent illness that prevents further treatment with the study drugs, investigator decision to remove subject from the study, subject decision to withdraw consent, noncompliance with trial treatment or procedure requirements, subject becomes pregnant or other administrative reasons. If treatment is changed due to progression of disease, each patient will be followed for 90 days after the end of treatment for ongoing monitoring for adverse events. If treatment is changed for reasons other than disease progression (withdrawal of

consent,), the patient will still be followed post-treatment for disease progression and survival analysis. In order to document overall survival data, all patients will be followed by telephone contact or at follow-up appointment until they die or they withdraw consent or it is decided that follow-up is no longer required by the sponsor-investigator.

Number of Centers: 1

Number of Patients:

36

Study Population:

Inclusion Criteria:

1. Written informed consent obtained from the patient prior to performing any protocol-related procedures, including screening evaluations.
2. Age ≥18 years at time of study entry.
3. Body weight >30kg.
4. Histologically or cytologically confirmed recurrent or metastatic HNSCC.
5. Not considered a candidate for other curative intent therapy (i.e. surgery/ RT) based on investigator clinical assessment and imaging.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
7. Adequate normal organ and marrow function as defined below:

   - Hemoglobin ≥9.0 g/dL

   - Absolute neutrophil count (ANC ≥1.5)

   - Platelet count ≥100 x 10^9/L

   - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology) who will be allowed only in consultation with their physician

- AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN

- Measured creatinine clearance (CL) >40 mL/min or calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976)

8. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months prior to study entry without an alternative medical cause. The following age-specific requirements apply:

   Women <50 years of age would be considered post-menopausal if: they have been amenorrheic for 12 months or more, they have been amenorrheic for 12 months following cessation of exogenous hormonal treatments, or if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

   Women ≥50 years of age would be considered post-menopausal if: they have been amenorrheic for 12 months or more, they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy.

9. Willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

10. Both male and female participants must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Exclusion Criteria:

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study.

2. Patients with nasopharyngeal and salivary gland tumors.

3. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

4. Prior exposure to immunotherapy drugs (PD-1, PDL-1, CTLA-4 inhibitors including durvalumab) AND to cetuximab regardless of whether they were given in combination or separately at differing time points. However a single exposure to either immunotherapy drugs OR cetuximab will not be considered to be exclusionary.

5. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) ≤ 14 days prior to the first dose of study drug (with the exception of cetuximab). If sufficient wash-out time has not occurred due to the schedule or pharmacokinetic properties of an agent, a longer wash-out period will be required, as agreed by the investigator.

6. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

   a. Patients with Grade ≥2 neuropathy will be evaluated for exclusion on a case-by-case basis by the treating investigator.

   b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or cetuximab may be included only after consultation with the PI.

7. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

8. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation ≤ 28 days of the first dose of study drug.

9. Major surgical procedure (as defined by the PI) ≤ 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], , systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc...]). The following are exceptions to this criterion:

    - Patients with diverticulitis or diverticulosis.

    - Patients with vitiligo or alopecia.

    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.

- Any chronic skin condition that does not require systemic therapy.

- Patients without active disease in the last 5 years may be included.

- Patients with celiac disease controlled by diet alone.

11. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

12. History of another primary malignancy except for:

    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

    - Adequately treated carcinoma in situ without evidence of disease

    - Another primary of Head and Neck is allowable as long as same HPV status (either both negative or both positive)

    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence

13. History of leptomeningeal carcinomatosis.

14. History of active primary immunodeficiency.

15. History of allogenic organ transplantation.

16. Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period or identified prior to signing the ICF.

    a. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their

treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ≤10mg/day of prednisone or its equivalent and anti-convulsant for at least 14 days prior to the start of treatment.

17. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from an ECG at screening.

18. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

19. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or cetuximab. The following are exceptions to this criterion:

    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

    - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.

21. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab

22. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

23. Known allergy or hypersensitivity to durvalumab and/or cetuximab or any excipient.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Patients will be monitored for adverse events, which will be graded in severity using the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Efficacy Assessments:

Radiographic imaging will be done every 8 weeks to assess response to treatment. Overall Response Rate (ORR) (RECIST v1.1) will be used as the primary efficacy end-point.

Statistical Methods and Data Analysis:

University of Cincinnati manages about 300 new cases of HNSCC per year, of which about 50 develop recurrent or metastatic disease. We plan to recruit a total of 36 patients with recurrent or metastatic HNSCC for our study. Previous studies have shown an ORR of 10% using durvalumab and 14.5% using cetuximab. In our study, where we will be using a combination of these 2 drugs, using a one-sided 0.05 alpha test, we expect to reach over 84% power to detect an ORR of 35 % against a null ORR of 14%, using Simon's two-stage design method in power calculation. Same studies have reported the rate of Grade≥3 adverse events (AEs) as 7% for durvalumab and 29.5% for cetuximab respectively. In our proposed study using the combination of durvalumab and cetuximab, we expect the rate Grade≥3 AEs of 30%. However, if during the first stage (first 13 patients), more than 50% ≥ Grade 3 adverse events are recorded, an early stopping rule will be employed for concerns of safety of the combination.

Investigational Product(s), Dose, and Mode of Administration:

Cetuximab 500 mg/m2 IV will be administered over 120 minutes on 2 weeks prior to starting the combination of durvalumab and cetuximab (unless the patient is already on cetuximab, they may continue without washout and without longer infusion time). Then 2-weeks later cetuximab 500 mg/m2 IV (administered over 60 minutes (±5 minutes)) and durvalumab 1500mg IV (approximately 1 hour (maximum 2 hours) after the completion of the cetuximab) will be administered. Thereafter cetuximab will be continued every 2 weeks and durvalumab every 4 weeks.

Note: If a patient's weight is ≤ 30kg the patient will receive durvalumab based on weight at 20 mg/kg Q4W until the weight is >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg.

SCHEDULE OF STUDY ASSESSMENTS

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.	**Screening [m]**	**All assessments to be performed pre-infusion unless stated otherwise**					
		Baseline [p]	**Every 4 weeks**	**Every other week**	**Every 8 weeks**	**Every 12 weeks**	**End of Treatment [n]**
Day	**-28 to 0**	**Day -14**	**Day 1 of the week**	**Day 1 of the week**			
Week	**-4 to 0**	**-2 (±3 days)**	**1, 5, 9, 13, etc.**	**3, 7 etc.**	**8, 16, 24, 32, 40, etc.**	**12, 24, 36, 48, etc.**	**30 Days after last dose**
			(±3 days)	**(±3 days)**	**(±7 days)**		**(±7 days)**
Written informed consent/assignment of patient identification number	X						
Demography and history of tobacco and alcohol use	X						
Archival tumor tissue sample available	X						
Medical and surgical history including previous treatments for HNSCC	X						
Hepatitis B and C; HIV	X						
Urine hCG or serum βhCG **a**	X		As clinically indicated				

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.	**Screening [m]**	**All assessments to be performed pre-infusion unless stated otherwise**					
		Baseline [p]	**Every 4 weeks**	**Every other week**	**Every 8 weeks**	**Every 12 weeks**	**End of Treatment [n]**
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		(±3 days)	**(±3 days)**	**(±3 days)**	**(±7 days)**		**(±7 days)**
Durvalumab administration **b**			X (Durvalumab Q4W)				
Cetuximab administration		X	X (cetuximab Q2 weeks)	X (Cetuximab Q2 weeks)			
Follow-up Survival Assessment **c**						X	X
Physical examination **d**	X	X	X				X
Vital signs	X	X	X**e**	X			X
Weight (kg)	X	X	X				
ECG**f**	X		X				
Adverse event/serious adverse event assessment	X	X	X	X	X	X	X **g**
Concomitant medications	X	X	X	X	X	X	X
ECOG performance status **h**	X	X	X				X

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.	**Screening [m]**	**All assessments to be performed pre-infusion unless stated otherwise**					
		Baseline [p]	**Every 4 weeks**	**Every other week**	**Every 8 weeks**	**Every 12 weeks**	**End of Treatment [n]**
Day	**-28 to 0**	**Day -14**	**Day 1 of the week**	**Day 1 of the week**			
Week	**-4 to 0**	**-2 (±3 days)**	**1, 5, 9, 13, etc.**	**3, 7 etc.**	**8, 16, 24, 32, 40, etc.**	**12, 24, 36, 48, etc.**	**30 Days after last dose**
			(±3 days)	**(±3 days)**	**(±7 days)**		**(±7 days)**
Serum lipase, amylase and GGT[h]	X		X				X
Serum chemistry (complete clin.chem. Panel, including liver function tests- AST, ALT and ALP, magnesium and LDH) [h]	X	X	X				X
Serum Magnesium level				X			
Hematology [h]	X	X	X				X
Thyroid function tests (TSH and fT3 and fT4) [i]	X	X	X				X
Urinalysis [j]	X		X				X
Coagulation parameters [k]	X	As clinically indicated	As clinically indicated				X

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.	**Screening [m]**	**All assessments to be performed pre-infusion unless stated otherwise**					
		Baseline [p]	**Every 4 weeks**	**Every other week**	**Every 8 weeks**	**Every 12 weeks**	**End of Treatment [n]**
Day	**-28 to 0**	**Day -14**	**Day 1 of the week**	**Day 1 of the week**			
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			(±3 days)	**(±3 days)**	**(±7 days)**		**(±7 days)**
Flow cytometry collection of whole blood PBMCs[o]	X	X	X[l]				
Tumor assessment (CT or MRI to include all sites of disease)	X				X		

[a] Pre-menopausal female subjects of childbearing potential only. Must be performed within 72 hours of first clinical trial treatment.

[b] If a subject's weight falls to 30 kg or below the subject should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight increases >30 kg, at which point the subject should start receiving the fixed dosing of durvalumab 1500mg. On days that both cetuximab and durvalumab are given, cetuximab will always be given first. For the first cycle, there should be 1 hour with max of 2 hours between cetuximab and durvalumab infusions. If no concerns or toxicity after first cycle, durvalumab may be given immediately after cetuximab for subsequent infusions. Durvalumab will be given until disease progression. Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) assessments. Subsequent time between 2 consecutive doses of durvalumab cannot be less than 22 days, based on the half-lives of durvalumab.

[c] Phone call or clinic assessment is acceptable to assess for survival status. Survival will be confirmed on an annual basis from the date of the subjects 30 day safety visit.

[d] Full physical examination at baseline; targeted exams every other week for the first month, then monthly.

[e] For the FIRST infusion of durvalumab and cetuximab given together, subjects will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1-hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes)

- If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.
- For first dose of cetuximab and first dose of cetuximab and durvalumab combined, , patients should be monitored for 30 minutes after infusion. If they do not have a reaction, this can be omitted for subsequent cycles.

[f] ECGs will be done in triplicate during screening. On cycle 1 Day1 ECG will be done prior to the start of the first study treatment **and a second ECG will be taken 0-3hrs after administration of the combination is completed in the first cycle only.** Thereafter ECGs will be done only as clinically indicated. Screening and any abnormal ECGs will be performed in triplicate spaced at least 5 min apart. See section 8.2.2 for timing and more detail on ECGs.

[g] Adverse events should be recorded 30 days +/-3 days after last study treatment and reassessed at 90 days +/- 3 days unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study.

[h] Screening laboratory tests and ECOG must be within 10 days of first clinical trial treatment (first dose of cetuximab. For subsequent cycles, if laboratory assessments and ECOG are performed within 3 days prior to Day 1 of the cycle they do not need to be repeated at Day 1 for each cycle. Results for safety bloods must be available and reviewed before commencing an infusion. Depending on the profile of the combination agent, the frequency of the hematology, serum chemistry and LFT testing may need to be increased to every two weeks. Refer to Table 4 for a complete listing of all labs (e.g., GGT, LDH etc…).

[i] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[j]. Urinalysis performed at Screening, first dose of cetuximab, and every 4 weeks and as clinically indicated.

[k]. Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

[l]. Pharmacodynamic blood draws to be collected at screening, before initiation of Durvalumab week 1 and again week 5 only for a total of 3 time points.

[m]. Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria and they have not yet started treatment. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects may be re-screened indefinitely at the discretion of the sponsor-investigator.

[n]. The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All required procedures may be completed within ±7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit. If patient has adverse effects related to study drugs, repeat evaluations should occur at months 2 and 3 +/- 1 week. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

o. PBMCs can be collected either at screening or prior to first dose of cetuximab.

[p]. Day -14 dose of cetuximab should be skipped if the subject is continuing on prior standard of care cetuximab. Can proceed with cycle 1. 1st dose should be given 2 weeks prior to durvalumab +/- 3 days.

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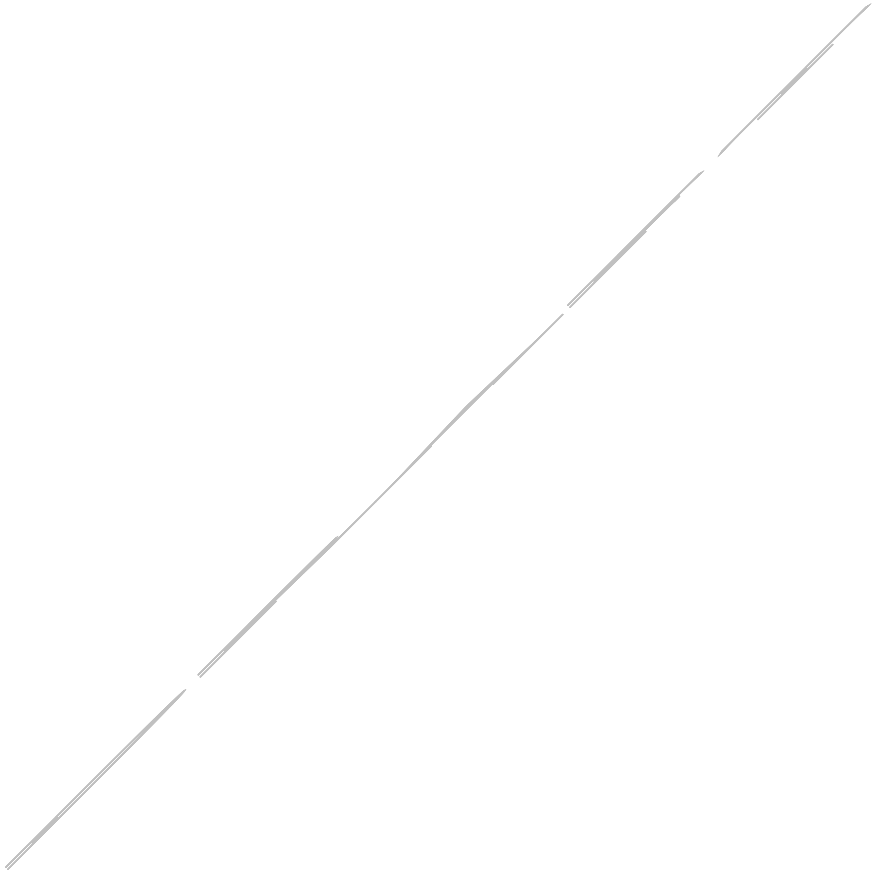


ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CRT	Chemoradiotherapy
CSR	Clinical study report
CT	Computed tomography

Abbreviation or special term	Explanation
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell cancer
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin

Abbreviation or special term	Explanation
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2

Abbreviation or special term	Explanation
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT	Radiation therapy
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone

Abbreviation or special term	Explanation
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease background

Head and neck squamous cell cancer (HNSCC) is the sixth most common cancer type worldwide and accounts for approximately 350,000 deaths per year.[1,2] Approximately 30 to 40% of patients with HNSCC present with stage I or II (early stage) disease.[3] In general, these patients are treated with either primary surgery or definitive radiation therapy (RT).[3] However, patients who present with advanced stage disease (Stage III or IV) not only pose a treatment challenge but also have a higher risk of both local recurrence and distant metastasis. Combined modality approaches (surgery, RT, and/or chemotherapy) are generally required to optimize the chance for long-term disease control for patients with advanced stage disease. These combined modality approaches include primary surgery followed by postoperative RT or concurrent chemoradiotherapy (CRT), induction chemotherapy (addition of chemotherapy prior to surgery and/or RT), concurrent CRT without surgery, or sequential therapy (induction chemotherapy followed by concurrent CRT) without surgery. Despite advances in the treatment of localized HNSCC, 15 to 50% of patients will develop recurrent disease,[4] which is further, complicated by lack of reliable salvage treatment options. Tissues of the head and neck such as skin, nerves, blood vessels, and spinal cord normally receive maximally tolerated radiation doses during the initial course of RT, therefore, re-irradiation exposes these tissues to more toxicities and complications. Subsequent surgery may not be possible due to previous surgeries and anatomical logistics. Therefore, upon relapse, palliative chemotherapy, using either single or multiple agents (often with Epidermal Growth Factor Receptor (EGFR) inhibitors like cetuximab), becomes the mainstay of management.[5] Even though expression of the EGFR is seen in up to 80% of HNSCC cells, overall response is only 15-20%.[6] Therefore novel drug combinations with Cetuximab are needed to increase its efficacy in a safe manner. For example cetuximab is known to affect immune checkpoints in both circulating and intra-tumoral lymphocytes. Adding check-point inhibitors to cetuximab may help increase its efficacy. Our

trial represents one such effort, where we will be testing the combination of cetuximab with the Programmed Death-Ligand-1 (PDL-1) inhibitor durvalumab.

1.2 Immunotherapies

The role of an intact immune surveillance in monitoring the outgrowth of neoplastic transformation has been delineated in recent years.[7] There have been several studies to suggest that accumulation of tumor-infiltrating lymphocytes (TILs) in cancer tissue is indicative of the host immune response to tumor antigens.[8] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.[8,9]

Novel immunotherapeutic strategies can enhance antitumor T-cell immunity by interrupting signals generated by immune checkpoint proteins. Programmed cell death-1 (PD-1, CD279), is an example of one such checkpoint protein, which is expressed on activated T cells; when bound by its ligand, programmed cell death ligand-1 (PD-L1, B7 homolog 1, CD274) on tumor cells, under healthy conditions helps to down-modulate unwanted or excessive T-cell mediated immune responses, including autoimmune reactions.[10]

PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor[11] and to CD80[12]. PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. (Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating IC. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination. PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated.[12,13]

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism. [14]

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients[15,16,17,18,19,20] with responses that tend to be more pronounced in patients with tumors that express PD-L1. [21,22,23] In addition, high mutational burden e.g., in bladder carcinoma[24] may contribute to the responses seen with immune therapy.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies while Nivolumab and Pembrolizumab, two anti-PD-1 agents and Atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1class shows clinical activity in a wide range of tumor types.

1.2.1 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ).[14]

To date, more than 6000 patients have been exposed to 1 or more doses of durvalumab in ongoing open-label AstraZeneca-or MedImmune-sponsored Phase I-III monotherapy and combination therapy studies across all indications. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.2.2 Cetuximab

Cetuximab, a chimeric human-mouse immunoglobulin G1 kappa monoclonal antibody, is directed against the extracellular ligand-binding domain of EGFR. This drug has shown efficacy in the recurrent and metastatic setting and is also approved for use in combination with radiation therapy in locally advanced HNSCC, in the curative setting. Cetuximab has been to shown to exert immunomodulatory effects via several mechanisms. On binding to EGFR, cetuximab results in an increased tumor-antigen specific T-cell activation (mediated by interaction with the antigen presenting cells). Majority of its effect is mediated via activation of natural killer (NK) cells and antibody-dependent cell-mediated cytotoxicity (ADCC). In addition to their ability to mediate ADCC, cetuximab-activated NK cells, secrete cytokines, such as IFN-γ MCP-1, MIP-1β that inhibit tumor cell proliferation, enhance antigen presentation, and chemokines such as IP10 and MIG that aid in the chemotaxis of T cells.[6]

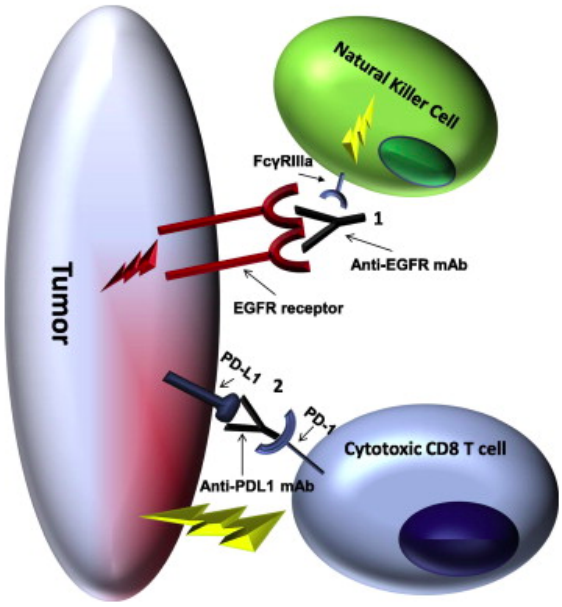


Figure 1. Comparison of the effects of anti-EGFR mAb and anti-PD-L1 mAb. IgG1 Anti-EGFR mAb (cetuximab) binds to the extracellular domain of the EGFR receptor leading to downregulation of EGFR on the cell surface and blockade of EGFR-mediated signaling, resulting in cell cycle arrest and apoptosis. Additionally, interaction between Fc gamma receptor IIIa (FcγRIIIa) and IgG1 anti-EGFR mAb (cetuximab) causes activation of NK cells leading to antibody-dependent cellular cytotoxicity (ADCC). Binding of anti-PD-L1 mAb to PD-L1 expressed on tumor, blocks the ligation of PD-1 by PD-L1 allowing the cytotoxic T cell to remain active and attack the tumor.

1.2.3 Rationale for durvalumab in combination with cetuximab

Treatment with cetuximab has been shown to alter the expression of checkpoint receptors on circulating and intratumoral TILs. Specifically, the frequency of Treg suppressor cells that

express CTLA-4 and PD-1 are enriched in the tumor microenvironment.[26] Furthermore, Cetuximab therapy increased the frequency of $CD4^{+}CD25^{hi}CD39^{+}FOXP3^{+}$ Treg (P = .01), indicating that this treatment expands Treg in patients with HNSCC.[27] Recent data in non–small-cell lung carcinoma indicate that the EGFR pathway may contribute to regulation of PD-L1 expression,[28] a finding corroborated in HNSCC by Concha and colleagues.[29] There is emerging data to support the use of checkpoint inhibitory monoclonal antibodies in treating patients with HNSCC, either to deplete Treg or to disrupt the PD-1: PD-L1 suppressive signal transmitted to CD8+ effector T lymphocytes. Suppressed NK cells and T cells express the negative regulatory PD-1 receptor, at higher levels and generate a greater inhibitory signal in tumor-infiltrating lymphocytes. This provides a strong rationale for combining cetuximab with anti–PD-1 monoclonal antibody therapy. The addition of PDL-1 inhibitor durvalumab to standard of care cetuximab may increase the efficacy of cetuximab in patients with HNSCC.

1.3 Research hypothesis

Addition of durvalumab to standard of care cetuximab in recurrent/metastatic HNSCC will result in increased response rates and the combination is tolerable.

1.4 Rationale for conducting this study

1.4.1 Rationale for the trial and selected subject population

At the University of Cincinnati, we treat at least 300 new head and neck cancer patients each year. Many of these patients will eventually develop relapse and/ or metastasize. Upon local relapse, the standard of care is often salvage surgical resection or RT dependent on the patient's performance status and prior dose of radiation used. If the patients are not amenable to curative-intent radiation or surgery, they are approached in a similar manner as patients with metastatic disease. Palliative chemotherapy, using either single or multiple agents (often with Epidermal Growth Factor Receptor (EGFR) inhibitors), becomes the mainstay of management. However response rates to EGFR inhibitor cetuximab are poor at 15-36% with overall survival of only 5-11 months. Our rationale of studying the combination of cetuximab with other novel agents like PDL1 inhibitor durvalumab is to potentially increase its efficacy without causing more adverse effects.

1.4.2 Durvalumab + Cetuximab combination therapy dose rationale

The durvalumab + cetuximab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and cetuximab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

1.4.2.1 Durvalumab

Rationale for q2 week vs q4 week dosing (Pharmacokinetic/ Pharmacodynamic data)

Pharmacokinetic (PK) simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. These data are in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-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 WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others[30,31,32,33] and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies.[31] 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-patient variability in pharmacokinetic/pharmacodynamics parameters.[32]

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic 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.

1.4.2.2 Cetuximab

Rationale for dosing

Based off recent FDA guidance, the recommended dose is 500 mg/m2 administered initially as 120-minute intravenous infusion (maximum infusion rate 10 mg/min), and the recommended subsequent dose every 2 weeks (all other infusions) is 500 mg/m2 infused over 60 minutes (maximum infusion rate 10 mg/min). Shin et al [34] conducted a Phase Ib study with Cetuximab in combination with cisplatin in patients with recurrent SCCHN. Twelve patients who had high levels of EGFR expression and tumors easily accessible for repeated biopsies (pre-therapy, 24 hours after first infusion, and 24 hours before third infusion) were entered at three different dose levels of cetuximab (100 mg/m2 as a loading dose with maintenance doses at 100 mg/m2 weekly; 500 mg/m2 as a loading dose with maintenance doses at 250 mg/m2 weekly; and 400 mg/m2 as a loading dose with maintenance doses at 250 mg/m2 weekly). The loading dose of 400 mg/m2 followed by a maintenance dose of 250 mg/m2 achieved a high percentage of saturation of EGFR in tumor tissue, and these doses were recommended for Phase II or III clinical trials.

The approval for the 500mg/m2 twice weekly dose was based on population pharmacokinetic analyses, in which the predicted exposures of cetuximab 500 mg/m2 twice weekly were compared to the predicted exposures of cetuximab 250 mg once weekly. Among the trials studied were BONNER (NCT00968435) and EXTREME (NCT00122460) for HNSCC and CRYSTAL (NCT00154102) and Study CA225-025 (NCT00079066) for KRAS wild-type, EGFR–expressing metastatic CRC. The population pharmacokinetic analyses were supported by pooled analyses of overall response rates, progression-free survival, and overall survival.

Pharmacokinetic data

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics.[35] The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m2 as the dose increased from 20 to 200 mg/m2, and at doses >200 mg/m2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m2. Following the recommended dose regimen (400 mg/m2 initial dose; 250 mg/m2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours).**Clinical Studies**

There are several studies that have studied cetuximab use in various setting in HNSCC. Bonner et al[36] and Ang et al[37] elucidated the role of cetuximab in combination with RT or CRT

respectively in phase III clinical trials in locally advanced HNSCC, while Vermorken et al[38] and Burtness et al[39] studied cetuximab in combination of Cisplatin-5FU and cetuximab in combination with Cisplatin respectively in phase III clinical trials relapsed/ metastatic HNSCC.

1.5 Benefit-risk and ethical assessment

1.5.1 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

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. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These risks can include gastrointestinal AEs such as colitis and diarrhea, pancreatitis, pneumonitis/interstitial lung disease (ILD), renal AEs such as nephritis and increases in creatinine, hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, endocrinopathies such as hypo- and hyper-thyroidism, hyophysitis, adrenal insufficiency, diabetes mellitus type I and diabetes insipidus, and neurotoxicities such as myasthenia gravis and Guillain-Barre syndrome.

Durvalumab

The identified risks with durvalumab monotherapy include the following: pneumonitis, ALT/AST increased, hepatitis, diarrhea, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypopituitarism, type 1 diabetes mellitus, blood creatinine increased, nephritis, rash, pruritus, dermatitis, myocarditis and infusion related reaction.

Potential risks for durvalumab include pancreatitis, increased amylase and lipase, hypophysitis, neuropathy/neuromuscular toxicity (e.g. Myasthenia gravis, Guillain Barre syndrome), other rare events with potential immune mediated etiology, e.g. pericarditis and uveitis.

Hypersensitivity reactions including anaphylaxis and allergic reaction, cytokine release syndrome, immune complex disease. Also, serious infections.

Further information on these risks can be found in the current version of the durvalumab IB.

Cetuximab

The most common adverse reactions in cetuximab clinical trials (incidence >=25%) include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. The most serious adverse reactions with cetuximab include infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.[37,36,39,38] Across the studies cited above, cetuximab was discontinued in 3–10% of patients because of adverse reactions. Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anemia.

Durvalumab + Cetuximab

The safety of durvalumab + cetuximab combination therapy will be evaluated in this trial and we expect a manageable toxicity profile. The potential risks with this combination of are similar to those for durvalumab and cetuximab monotherapy. We are aware though that given the proposed immune mechanisms of cetuximab, we might see an increase in immune mediated toxicities but subjects will be monitored closely.

1.5.2 Overall benefit-risk

Overall by combining durvalumab with cetuximab in patients with metastatic/ recurrent HNSCC could result in increase in the efficacy of cetuximab. EGFR inhibitors alter the expression of PD1 in the tumor infiltrating lymphocytes and the tumor microenvironment, and the addition of PDL1 inhibitors could help overcome the resistance to cetuximab. Since the two drugs work through different mechanisms, as described in the preceding sections, their adverse effects are not likely to be additive.

2 STUDY OBJECTIVE

2.1 Primary objective

Primary efficacy objective: To determine the objective response rate (ORR) of the combination of durvalumab and cetuximab using RECIST 1.1 in subjects with recurrent and/or metastatic HNSCC.

Hypothesis: The combination of durvalumab and cetuximab in patients with recurrent and/or metastatic HNSCC will result in a clinically meaningful ORR of greater than 35%.

2.2 Secondary objective(s)

1. To determine the safety and tolerability of durvalumab intravenously (IV) combined with standard of care cetuximab in patients with recurrent and/or metastatic HNSCC.
2. To determine disease control rate (DCR = CR [complete response] + PR [partial response] + SD [stable disease]) at 6 months in patients receiving durvalumab and cetuximab with recurrent and/or metastatic disease.
3. To estimate the progression-free survival (PFS) using RECIST 1.1 in all patients receiving durvalumab and cetuximab with recurrent and/or metastatic HNSCC.
4. To estimate the overall survival (OS) separately in all patients receiving durvalumab and cetuximab with recurrent and/or metastatic HNSCC.
5. To estimate the duration of response (DOR) in all patients receiving durvalumab and cetuximab with recurrent and/or metastatic HNSCC.

2.3 Exploratory objective(s)

1. To explore potential predictive biomarkers of efficacy, such as response, PFS and OS, in subjects receiving a combination of cetuximab and durvalumab by analyzing tumor specimens for proteins involved in regulating immune responses including PD-L1 and PD-L2.

2. Evaluate archival tumor specimens for CD4, CD8 and T reg ratios in order to determine immune composition in the tumor microenvironment and tumor. The study will also determine immune cell activity with KI-67 and granzyme expression in tumor.

3. To study peripheral blood T cell response after anti-PDL-1 treatment by multi-color flow-cytometry to determine type of peripheral immune response.

3 STUDY DESIGN

3.1 Overview of study design

This study will be a single center, nonrandomized, single-cohort trial of durvalumab and cetuximab in patients with recurrent and/or metastatic HNSCC. We plan to enroll approximately 36 subjects to examine the safety and early efficacy of combining durvalumab with cetuximab in this patient population.

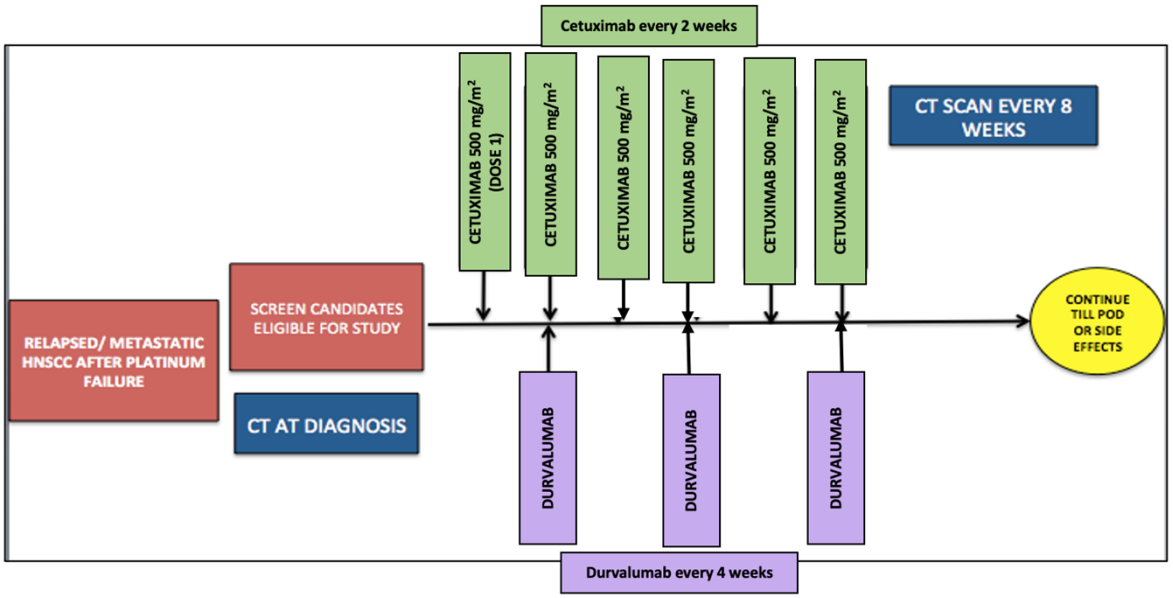
Enrolled subjects will receive standard of care cetuximab 500 mg/m2 IV over 120 minutes on Day -14 as /baseline dose (this will be skipped if subjects are already on standard of care cetuximab); then starting 2 weeks later cetuximab 500 mg/m2 IV over 60 minutes every 2 weeks followed by durvalumab 1500 mg every 4 weeks IV. This regimen will be continued until progression of disease or development of intolerable side effects, intercurrent illness that prevents further treatment with the study drugs, investigator decides to remove subject from the study or subject decides to withdraw consent, noncompliance with trial treatment or procedure requirements, subject becomes pregnant or other administrative reasons. Subjects will be followed weekly during treatment for the first month, then monthly while on treatment. Radiographic imaging will be done every 8 weeks to assess response. ORR (RECIST v1.1) will be used as the primary efficacy end-point.

Subjects will be monitored for adverse events, which will be graded in severity using the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If treatment is changed for progression of disease, each subject will be followed for 90 days after the end of treatment for ongoing monitoring for adverse events. If treatment is changed for reasons other than disease progression (withdrawal of consent, being lost to follow up etc.), subjects will also be followed post-treatment until disease progression. Subjects may continue to receive durvalumab + cetuximab beyond confirmed PD in the absence of clinically significant deterioration and if the investigator believes that subjects continue to receive benefit from treatment. In order to document overall survival data, all subjects will be followed by telephone contact (or via clinic visits) until death or withdrawal of consent.

Correlative studies including PDL1 levels, tumor infiltration of CD4+ and CD8+ T-cells will be done using archived biopsy samples as well as blood samples which will be collected at screening (or prior to baseline day -14), before initiation of durvalumab week 1 and again at week 5 only for a total of 3 time points.

3.2 Study schema

Figure 2. Study schema



4 PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWL

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Any waiver of eligibility criteria must be approved by the sponsor-investigator and approved by the IRB of record prior to enrollment.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1) Written informed consent obtained from the patient prior to performing any protocol-related procedures, including screening evaluations
2) Age ≥18 years at time of study entry
3) Body weight >30kg
4) Histologically or cytologically confirmed recurrent or metastatic HNSCC
5) Not a candidate for other curative intent therapy (i.e. surgery/ RT) as determined by the treating investigator
6) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
7) Adequate normal organ and marrow function as defined below:

    - Hemoglobin ≥9.0 g/dL

    - Absolute neutrophil count (ANC ≥1.5)

    - Platelet count ≥100 x 10^9/L

    - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician

    - AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN

    - Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976)

Males:

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

Females:

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

8) Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months prior to study entry without an alternative medical cause. The following age-specific requirements apply:

   Women <50 years of age would be considered post-menopausal if: they have been amenorrheic for 12 months or more, they have been amenorrheic for 12 months following cessation of exogenous hormonal treatments, or if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

   Women ≥50 years of age would be considered post-menopausal if: they have been amenorrheic for 12 months or more, they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy.

9) Willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

10) Both male and female participants must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1) Involvement in the planning and/or conduct of the study

2) Patients with nasopharyngeal and salivary gland tumors

3) Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

4) Prior exposure to both immunotherapy drugs (PD-1, PDL-1, CTLA-4 inhibitors including durvalumab) AND prior exposure to cetuximab regardless if they were given in combination or separately. However single exposure to either immunotherapy drugs OR cetuximab will not be considered to be exclusionary.

5) Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤ 14 days prior to the first dose of study drug with the exception of cetuximab. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by the investigator.

6) Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

   a. Patients with Grade ≥2 neuropathy will be evaluated for exclusion on a case-by-case basis by the treating investigator.

   b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or cetuximab may be included only after consultation with the PI.

7) Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

8) Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation ≤ 28 days of the first dose of study drug.

9) Major surgical procedure (as defined by the PI) ≤ 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

10) Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

   - Patients with diverticulitis or diverticulosis

   - Patients with vitiligo or alopecia

   - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

- Any chronic skin condition that does not require systemic therapy

- Patients without active disease in the last 5 years may be included

- Patients with celiac disease controlled by diet alone

11) Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

12) History of another primary malignancy except for:

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

- Adequately treated carcinoma in situ without evidence of disease

- Another primary of Head and Neck is allowable as long as same HPV status (either both negative or both positive)

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence

13) History of leptomeningeal carcinomatosis.

14) History of active primary immunodeficiency.

15) History of allogenic organ transplantation.

16) Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period or identified prior to signing the ICF.

a. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use

of steroids, or are stable on a steroid dose of ≤10mg/day of prednisone or its equivalent and anti-convulsant for at least 14 days prior to the start of treatment.

17) Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from an ECG at screening.

18) Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

19) Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or cetuximab. The following are exceptions to this criterion:

    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

    - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

20) Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.

21) Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab

22) Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

23) Known allergy or hypersensitivity to cetuximab or durvalumab or any excipient

4.3 Withdrawal of patients from study treatment and/or study

4.3.1 Permanent discontinuation of study treatment

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1) Withdrawal of consent or lost to follow-up.
2) Adverse event that, in the opinion of the sponsor-investigator, contraindicates further dosing.
3) Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
4) Pregnancy or intent to become pregnant.
5) Any AE that meets criteria for discontinuation as defined in Section 10.
6) Grade ≥3 infusion reaction.
7) Subject noncompliance that, in the opinion of the sponsor-investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
8) Initiation of alternative anticancer therapy including another investigational agent.
9) Confirmation of PD and the sponsor-investigator determines that the subject is no longer benefiting from treatment with durvalumab + cetuximab. Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.
10) Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10 and **Error! Reference source not found.** or **Error! Reference source not found.**, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone as an alternative.

4.3.2 Withdrawal of consent

Subjects are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Subjects who withdraw consent for further participation in the study will not receive any further IP or further study observation, *with the exception of follow-up for survival*, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the subject may be offered additional tests or tapering of treatment to withdraw safely.

A subject who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AEs. The sponsor-investigator will follow up AEs outside of the clinical study.

If a subject withdraws consent, they will be specifically asked if they are withdrawing consent to:

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.4 Replacement of patients

Subjects who are unfit or unwilling to continue study after enrollment will be replaced. Any subject who does not complete at least 1 dose of durvalumab and cetuximab will also be replaced.

5 INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab and Cetuximab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the sponsor-investigator as a solution for infusion after dilution. Cetuximab will be given as standard of care and will be ordered through commercial sources.

5.2 Formulation/packaging/storage

Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 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 10.0 mL. Investigational product vials are stored at 2° C to 8° C (36° F to 46° F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Cetuximab

Cetuximab will be supplied by commercial sources.

5.3 Dose and treatment regimens

5.3.1 Treatment regimens

Durvalumab + Cetuximab combination therapy

Subjects will receive first/ baseline dose of cetuximab 500 mg/m2 IV over 120 minutes on Day -14 (this will be skipped if subjects are already on standard of care cetuximab); then starting 2 weeks later cetuximab 500 mg/m2 IV over 60 minutes every 2 weeks and durvalumab (MEDI4736) 1500 mg every 4 weeks IV until confirmed disease progression or unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a subject's weight falls to 30 kg or below the subject should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight increases >30 kg, at which point the subject should start receiving the fixed dosing of durvalumab 1500mg.

Cetuximab infusion will be administered prior to the durvalumab on days the subject receives both medications. The first dose of cetuximab should be administered over 120 minutes (±5 minutes). Subsequent doses of cetuximab should be administered over 60 minutes (±5 minutes). Durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the completion

of the cetuximab on first combination day (week 1). In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. If there are no clinically significant concerns after the first cycle, then, all other doses of durvalumab can be given immediately after the cetuximab infusion has finished.

5.3.2 Duration of treatment and criteria for retreatment

All treatment with durvalumab (MEDI4736) and cetuximab combination therapy will be administered until confirmed progression of disease or unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.Subjects may continue to receive durvalumab + cetuximab beyond confirmed PD in the absence of clinically significant deterioration and if the investigator believes that subjects continue to receive benefit from treatment.

Subjects with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will **not** be eligible for continuing durvalumab (MEDI4736). If applicable for all subjects who completed the first 24-month period of treatment with the immunotherapy agents and had CR, PR, or SD at completion, retreatment during follow up would be offered on the basis of a subject having objective RECIST 1.1 disease progression with or without confirmation.

For all subjects who are treated through progression, or subjects who achieve disease control (i.e., CR, PR, or SD) at 24 months and restart treatment upon evidence of PD during follow-up, the sponsor-investigator should ensure subjects do not have any significant, unacceptable or irreversible toxicities that indicate continuing or restarting treatment would not further benefit the subject.

Subjects meeting the retreatment criteria below will follow the same treatment guidelines followed during the initial 24-month treatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Subjects who meet the criteria for retreatment may only receive retreatment once.

Subjects receiving the durvalumab (MEDI4736) + cetuximab combination therapy may undergo retreatment as described below:

For all subjects who are treated through progression and for subjects who are restarting durvalumab (MEDI4736), the sponsor-investigator should ensure that:

- The subject does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the subject.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >2.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.
- The subject still fulfills the eligibility criteria for this study with the exception of exclusion criteria to not have received prior anti–PD-L1 agents. Subjects must also agree to re-consenting to restart durvalumab (MEDI4736) therapy.
- After the defined treatment period of 24 months, the subject should not have received any intervening systemic anticancer therapy after their assigned treatment discontinuation.
- For option of retreatment after defined treatment period, provided the subject has had a baseline tumor assessment within a maximum of 28 days prior to restarting their assigned treatment; all further scans should occur with the same frequency as during the initial 24 months of treatment (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment).

During the retreatment period, subjects will resume durvalumab (MEDI4736) dosing at 1500mg Q4W (if still receiving cetuximab, they may remain on 500 mg/m^2 every 2 weeks; cetuximab may also be restarted if previously discontinued and should follow same schedule as at beginning of study with re-administration of baseline dose of 500 mg /m2 prior to starting combination). Subjects will then continue these drugs until disease progression or intolerance to drugs.

Subjects who the sponsor-investigator determines may not continue treatment after PD will be followed for survival. Subjects who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed until confirmed disease progression and for survival.

5.3.3 Study drug preparation of Durvalumab and Cetuximab

The dose of durvalumab is 1500 mg Q4W. Cetuximab will be administered at the standard dose of 500 mg/ m^2 (first dose will be skipped if subjects are already on standard of care cetuximab) every 2 weeks. Rounding of doses to the nearest 10mg is acceptable.

Preparation of Durvalumab doses for administration with an IV bag

Total time from needle puncture of the durvalumab (MEDI4736) 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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) 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. Add 30.0 mL of durvalumab (MEDI4736) (i.e., 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing (for patients ≤30 kg) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) 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.

The IV line will be flushed with a volume of IV diluent 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.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

Do not co-administer other drugs through the same infusion line.

Preparation of Cetuximab doses for administration with an IV bag

Total time from needle puncture of the cetuximab 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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A baseline/ dose of 500 mg /m^2 will be administered on day -14 over 120 minutes as an IV infusion followed by 500 mg /m^2 IV over 60 minutes every 2 weeks. The drug is not to be administered as an intravenous push or bolus. It is to be administered via infusion pump or syringe pump, to not exceed an infusion rate of 10 mg/min. The drug is administered through a low protein binding 0.22-micrometer in-line filter. Each single-use 100mg/ 50 ml vial, 200mg/ 100 vial at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride,1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP. It should not be shaken or diluted prior to administration.

In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Any unused portion of the drug must be discarded.

5.3.4 Monitoring of dose administration

Subjects will be monitored during and after the infusion as described in the SOE for the first infusion with assessment of vital signs for 30 minutes after completion of subsequent infusions.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. For management of subjects who experience an infusion reaction, please refer to the toxicity and management guidelines in **Error! Reference source not found.**.

5.3.5 Accountability and dispensation

Clinical supplies will be stored in a secure, limited access location under the storage conditions specified on the label. At the University of Cincinnati recording of the receipt and dispensing of trial medication will be handled by IDS Pharmacy staff.

5.3.6 Disposition of unused investigational study drug

The sponsor-investigator is responsible for keeping accurate records of the clinical supplies received from AstraZeneca or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the sponsor-investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6 TREATMENT PLAN

6.1 Patient enrollment

Potential subjects will be enrolled but not randomized (open label treatment). They will be evaluated to determine if they fulfill entry requirements into the trial as set forth in eligibility requirements in Section 4.

Results of a test performed prior to the potential subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria and they have not yet started treatment. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

Procedures for handling subjects incorrectly enrolled

When a subject is incorrectly enrolled on the study and not yet initiated on treatment, they will be withdrawn from the study.

6.2 Dose modification and toxicity management

Durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab + cetuximab are provided in the Dosing Modification and Toxicity Management Guidelines in **Error! Reference source not found.**. Subjects should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune adverse events (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and cetuximab should be permanently discontinued (see Section 4.3 of this protocol and the Dosing Modification and Toxicity Management Guidelines in **Error! Reference source not found.**).

Following the first dose of IP, subsequent administration of durvalumab and cetuximab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in **Error! Reference source not found.**. These guidelines have been prepared to assist the sponsor-investigator in the exercise of their clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + cetuximab regimen by the investigator.

Dose reductions are not permitted for Durvalumab.

In case of doubt, the treating physician should consult with the sponsor-investigator.

Cetuximab Dose Modification Guidelines:
Dose reduction of cetuximab by 1 and, if needed, 2 dose levels (Table 2) will be allowed depending on the type and severity of toxicity encountered. Subjects requiring more than

2 dose reductions will be discontinued from the study and entered into the follow-up phase.

Cetuximab Available Dose Levels

Dose Level	Cetuximab dose
Starting Dose	500 mg/m2
-1	250 mg/m2
-2	150 mg/m2

*Cetuximab dose de-escalation below 150 mg/m2 is not allowed.

Cetuximab Hypersensitivity Reactions

Mild (Grade 1) hypersensitivity reactions (HSRs) characterized by mild pruritus, flushing, rhinitis, rash, and fever are treated with symptom-directed management, including cessation of infusion, administration of diphenhydramine 25 mg or similar, followed by famotidine 20 mg or similar if symptoms remain after diphenhydramine. Vital signs should be monitored every 15 minutes until symptoms resolve. Treatment may be restarted at the same rate at resolution of symptoms.

Moderate (Grade 2) HSRs consist of generalized pruritus, flushing, rash, back pain, dyspnea, hypotension, and rigors. The infusion should be stopped, and oxygen should be administered if the patient is experiencing dyspnea. Normal saline 500 mL bolus may be given if the patient is hypotensive (may repeat as needed). Diphenhydramine 50 mg (or similar) should be administered, followed by famotidine 20 mg (or similar) followed by hydrocortisone 100 mg (or similar) followed by meperidine 25 mg IV (if needed for rigors). Vital signs should be monitored frequently (such as every 2 minutes until stable, then every 15 minutes until symptoms resolve). Treatment may be restarted at resolution of symptoms.

Severe (Grade 3) HSRs are characterized by bronchospasm, generalized urticaria, hypotension, and angioedema. These HSRs should be managed by stopping the infusion and administering: normal saline 500 mL bolus (repeat as needed), epinephrine, diphenhydramine 50 mg IVP or similar, famotidine 20 mg IV or similar, hydrocortisone 100 mg IVP or similar, and albuterol 2.5 mg inhalation (for bronchospasms). Vital signs should be monitored frequently as above. If cetuximab is restarted, restart the infusion rate at 25% of original rate for 30 minutes, then increase to 50% of infusion rate for the remainder of the infusion. The infusion rate should be permanently reduced by 50%.

Life-threatening/disabling (Grade 4) HSRs consist of anaphylaxis, airway obstruction, shock,

cardiac arrest, or prolonged hypotension. Grade 4 HSRs require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

Cetuximab Infusion Reactions
Severe infusion reactions (Grade 4) require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

Cetuximab recommended dose modifications for infusion reactions:

- Reduce the infusion rate by 50% for National Cancer Institute Common Toxicity Criteria (NCI CTC v.5) Grade 1 or 2 and non-serious Grade 3 infusion reactions;
- Immediately and permanently discontinue cetuximab for serious infusion reactions, requiring medical intervention and/or hospitalization;
- Review the information found in the locally approved package insert for cetuximab
- If a subject experiences recurrent fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate.

Cetuximab Dermatological Toxicities
Subjects developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (Grade 3) acneiform rash. Treatment with topical and/or oral antibiotics (such as doxycycline 100 mg bid) should be considered.

In subjects with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab recommended dose modifications for severe (NCI CTCAE Grade 3 or 4) acneiform rash are described in the below table.

Cetuximab Dose Modifications in the Event of Acneiform Rash

	Toxicity (NCI CTCAE Grade 3 or 4, Version 5.0)

Severe Rash	Cetuximab	Outcome	Dose Modification
1st Occurrence	Delay Infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m2 Discontinue Cetuximab
2nd Occurrence	Delay Infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 200 mg/m2 Discontinue Cetuximab
3rd Occurrence	Delay Infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 150 mg/m2 Discontinue Cetuximab
4th Occurrence	Discontinue Cetuximab		

Cetuximab Pulmonary Adverse Effects
In the event of acute onset (Grade ≥2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until these symptoms have resolved to Grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the subject should be treated appropriately.

7 RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

The following restrictions apply while the subject is receiving study treatment and for the specified times before and after:

Female subject of child-bearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (**Error! Reference source not found.**) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + cetuximab combination therapy. Non-sterilized male partners of a female subject must use male condom plus spermicide throughout this period. Cessation of birth

control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should also refrain from breastfeeding throughout this period.

Male subjects with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + cetuximab combination therapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period (**Error! Reference source not found.**).

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months prior to the start of treatment without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent

surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in **Error! Reference source not found.**. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progesterone-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 1. Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Blood donation

Subjects should not donate blood while participating in this study, for at least 90 days following the last infusion of Durvalumab or Cetuximab.

7.2 Concomitant treatment(s)

The sponsor-investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any

concomitant medication(s), including herbal preparations, taken during the study should be recorded.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.2 for guidance on management of IP-related toxicities.

Permitted concomitant medications

Table 2. Supportive medications

Supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed below	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all subjects
Inactivated viruses, such as those in the influenza vaccine	Permitted

Excluded concomitant medications

Subjects, who, in the assessment by the sponsor-investigator, require the use of any of the mentioned treatments for clinical management other than those specified as allowed, should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describes other medications, which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

Table 3. **Prohibited concomitant medications**

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the subject is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the subject is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the subject is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications 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	*Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of* non-immunotherapy related events experienced by *the subject (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).*
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor-investigator

8 STUDY PROCEDURES

8.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

For all treatment subjects

- Tumor efficacy (RECIST 1.1) assessment dates are not affected by dose delays and remain as originally scheduled
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc. required for dosing should be performed within 3 days prior to dosing.
- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST 1.1) assessments. Subsequent time between 2 consecutive doses of Durvalumab cannot be less than 22 days, based on the half-lives of durvalumab.

8.1.1 Screening phase

Screening procedures will be performed up to 28 days before beginning Cetuximab (whether at Day -14 or Week 1), unless otherwise specified. All potential subjects must first read, understand, and sign the IRB approved ICF before any study-specific screening procedures can be performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to

the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

1. Informed Consent
2. Review of eligibility criteria
3. Medical history and demographics
4. Complete physical exam
5. ECOG Performance Status
6. Vitals signs, weight and height
7. 12-lead ECG (3 spaced at least 5 min apart)
8. Review of prior/concomitant medications
9. Imaging by CT/MRI
10. Acquire archival/ fresh tissue specimen
11. Clinical laboratory tests for:

Clinical chemistry (see

a. Table 4)
b. Hematology (see Table 5)
c. TSH
d. Coagulation (PT, PTT, INR)
e. Creatinine Clearance
f. Serum pregnancy test (for women of childbearing potential only)
g. Hepatitis serologies
h. Urinalysis (see Table 6)

8.1.2 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments.

8.1.3 End of treatment

End of treatment is defined as the last visit where the decision is made by the treating physician to discontinue treatment.

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

All required procedures may be completed within ±7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor-investigator ends the study or the subject withdraws consent for all participation.

8.2 Description of study procedures

8.2.1 Medical history and physical examination

Findings from medical history (obtained at screening) and physical examination related to disease shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical examinations may be utilized by the treating investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10.

8.2.2 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening (3 ECGs spaced 5 min apart) and at C1D1 one ECG will be done prior to dosing and a second will be done 0-3 hours after dosing. For all subsequent visits ECGs will only be done as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, or as clinically indicated, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding (except at screening when triplicate ECGs are already performed).

Situations in which ECG results should be reported as AEs are described in Section 10.3.1.

8.2.3 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded at each visit along with vital signs.

First infusion of both Durvalumab + Cetuximab

On the first infusion day (Cycle 1, week 2), subjects receiving durvalumab + cetuximab combination therapy will be monitored and vital signs collected/recorded prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from subjects before, during, and after the Cycle 1 Week 2 infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion ±5 minutes)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

A 1-hour observation period is recommended after the first infusion of durvalumab and cetuximab. In the observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only (Cycle 1 Week 2) and then for subsequent infusions only as clinically indicated.

Subsequent infusions after

BP, pulse and other vital signs should be measured, collected/recorded prior to the start of the infusion. Subjects should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should also be recorded.

8.2.4 Clinical laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see **Error! Reference source not found.** through Table 5).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test).

Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate CRF.

The laboratory variables to be measured are presented in

Table 4 (clinical chemistry), Table 5 (hematology), and Table 6 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies and HIV antibodies.

The following laboratory variables will be measured:

Table 4. Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	T3 free[c] (reflex)
Creatinine clearance[c]	T4 free[c] (reflex)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[c]	Lactate dehydrogenase
Glucose	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at screening, on Day -14 (unless screening laboratory assessments are performed within 10 days prior to Day -14 – baseline Dose), and if clinically indicated. Serum magnesium is to be collected at each cetuximab infusion.

[d] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone

Table 5. Hematology

Absolute neutrophil count	Absolute lymphocyte count
Hemoglobin	Platelet count

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Table 6. Urinalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

If a subject shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Error! Reference source not found.** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. 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.

All subjects should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP (see

Table 4).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded in the research record. Situations in which laboratory safety results should be reported as AEs are described in Section 10.3.5.

All subjects with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.3 Biological sampling procedures

8.3.1 Biomarker/pharmacodynamic sampling and evaluation methods

- Peripheral Blood Monocyte Cell (PBMC) Isolation:

40 mls of whole blood will be collected in EDTA purple top tubes prior to durvalumab and cetuximab administration at Screening, after 1st dose of cetuximab before initiation of durvalumab on week 1, as well as week 5 before durvalumab/ cetuximab combination and will be transferred at room temperature within 24 hours to Dr. Wise-Draper's laboratory at the Vontz Center. PBMCs and plasma will be separated by Ficoll centrifugation. Plasma will be frozen and stored at -80^{o} C. PBMCs will be either cryopreserved or immediately processed for flow cytometry and functional analysis. Please see procedure manual for full details.

- Immunohistochemistry/Immunofluorescence/RNAScope:

Archived tissue will be sent to the University of Cincinnati pathology department for analysis. FFPE and/or Frozen sections will be used to analyze the immune cell phenotype (markers include CD4, CD8, T reg, PD-1, PD-L1, granzyme expression and KI-67). Please see procedure manual for full details.

8.3.2 Archival tumor samples

Archival samples will be utilized. When archival samples are used to assess PD-L1 status, the age of the sample/date of collection will be captured. If the archival specimen is more than 3 years old, a fresh biopsy will be obtained if a subject is consented for biopsy for clinical reasons.

8.3.3 Fresh tumor biopsies

When possible, subjects will undergo a fresh tumor biopsy only if their archival specimen is more than 3 years old and if the subject is consented for biopsy for clinical reasons. Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis. Biopsy specimen will be sent to the University of Cincinnati pathology department for processing. FFPE and/or Frozen sections will be used to analyze the immune cell phenotype (markers include CD4, CD8, T reg, PD-1, PD-L1, granzyme expression and KI-67). Fresh biopsy and/or FFPE tissue will also undergo either whole genome sequencing or RNA sequencing to identify an inflammatory gene signature and/or mutational load that corresponds to subjects who respond versus those who did not.

8.3.4 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented if the sample has not yet been anonymized (link between subject name/identifiers and study code is still in place).

The Principal Investigator will:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

9 DISEASE EVALUATION AND METHODS

Although the clinical benefit of durvalumab and cetuximab has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus subjects will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Subjects with measurable disease will be assessed by standard criteria. For the purposes of this study, subjects should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 8 weeks following initial documentation of an objective response.

9.1 Antitumor Effect – Solid Tumors

For the purposes of this study, subjects should be re-evaluated for response every 8 weeks with CT scans. In addition to a baseline scan, confirmatory scans should also be obtained every 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following:

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

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., 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, we will implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence

of clinically significant deterioration. Treatment with durvalumab + cetuximab would continue between the initial assessment of progression and confirmation for progression.

- In addition, subjects may continue to receive durvalumab + cetuximab beyond confirmed PD in the absence of clinically significant deterioration and if the investigator believes that subjects continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab + cetuximab and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anticancer therapy other than durvalumab + cetuximab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.2 Definitions

- Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with durvalumab and cetuximab
- Evaluable for objective response: Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)
- Evaluable Non-Target Disease Response: subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

9.3 Disease Parameters

- Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
- Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and

should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. 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 is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. 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 one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.5 Response Criteria

a. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): There is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

b. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

c. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 7. For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

✓ See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 8. For Subjects with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
✓ 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Confirmation of progression guidelines are set for the following reasons:

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression

Confirmed objective disease progression refers to either of the following scenarios:

1. Clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); OR

2. In the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,

- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),

- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first PD by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a subject discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Following confirmed progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the follow-up schedules of assessments.

9.6 Duration of Response

1. Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

2. Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

3. Progression free Survival (PFS): Measured from the time of treatment allocation to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause. This will be a secondary endpoint.

10 ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

10.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

10.1.1 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

1. Results in death
2. Is immediately life-threatening
3. Requires in-patient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect in offspring of the patient
6. Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

10.1.2 Durvalumab adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

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 may require close monitoring. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If an Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the sponsor-investigator.

Reporting of AESI's to AstraZeneca

All AESI's are to be recorded in REDCAP and are reported to AstraZeneca. They should be reported as Serious Adverse Events to AstraZeneca if the AE meets the criteria for a SAE. If an adverse event of special interest does not meet the criteria for an SAE it should still be sent to AEmailboxclinicaltrialTCS@astrazeneca.com.

AESIs expected with Durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis // transaminase increases
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Intestinal perforations
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events

involving the eye, skin, hematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1). These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the study record. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

1. Physical examination

    – Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.

- SpO2

    – Saturation of peripheral oxygen (SpO2)

- Other items

- When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - ILD Markers (KL-6, SP-D) and β-D-glucan
    - Tumour markers: Particular tumour markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild) An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.2.1. A Grade 3 AE need

not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

The adverse event will be evaluated for whether it is likely to be related to the investigational drugs or not and this will be documented in the patient's chart and reported.

10.3 Recording of adverse events and serious adverse events

Please see the AESI section of the protocol for procedures for identification and submission of AESI's to AstraZeneca.

Adverse events will be recorded on the AE/SAE Form using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety via email.

The following variables will be collected for each AE:

In addition, the following variables will be collected for SAEs as applicable:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE

- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section **Error! Reference source not found.**.4
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab + cetuximab).

During the course of the study all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

10.3.2 Causality collection

The Investigator will assess causal relationship between the IPs and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in **Error! Reference source not found.**.

10.3.3 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

10.3.4 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

10.3.5 Adverse events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

10.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to **Error! Reference source not found.** for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.7 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

10.3.8 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

10.3.9 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be documented in the study record. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the PI and Astra Zeneca as an SAE within 24 hours. It should also be documented in the CRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the CRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the CRF. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10.3.10 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The sponsor-investigator are responsible for informing the IRB of the SAE as per local requirements.

The sponsor-investigator must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-##-#####)

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.3.10.1 Reporting of deaths to AstraZeneca

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab + cetuximab safety follow-up period must be reported to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the CRF. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

10.3.11 Other events requiring reporting

10.3.11.1 Overdose

Use of Durvalumab or Cetuximab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of Durvalumab or Cetuximab, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the CRF.

If an overdose of an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section **Error! Reference source not found.**. For other overdoses, reporting must occur within 30 days.

10.3.11.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

10.3.11.3 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

10.3.11.4 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + cetuximab combination therapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + cetuximab combination therapy, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the Institutional Review Board (IRB) prior to use.

10.4 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 10.3.10) and within 30 days for all other medication errors.

11 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Sample Size Justification/Statistical Analysis:

University of Cincinnati manages about 300 new cases of HNSCC per year, of which about 50 develop recurrent or metastatic disease. We plan to recruit a total of 36 patients with recurrent or metastatic HNSCC for our study. Previous studies have shown an ORR of 10% using durvalumab and 14.5% using cetuximab. [40] In our study, where we will be using a combination of these 2 drugs, we expect to reach over 84% power to detect an ORR of 35 % against a null ORR of 14%, using Simon's two stage design method in power calculation (Table1). Some studies cited above have reported the rate of Grade≥3 adverse events (AEs) as 7% for durvalumab and 29.5% for cetuximab respectively.[40,41] In our proposed study using the combination of durvalumab and cetuximab, we expect the rate Grade≥3 AEs of 30% but will accept up to 50% during the first stage. If more than 50% of patients experience ≥ Grade 3 AEs during the first stage (first 13 patients), then an early stopping rule will be employed due to concern of safety.

Table 9. Simon's 2 state design and power

H0: π=π0	H1: π=π1	***n***	n_1	r_1	r_2	**Type 1 Error**	***Power***	EN_0	**Probability of early stopping**	**Interval for *w***	**Comment**
π0=14%	π1=35 %	36	13	2	8	0.0429	0.8483	19.2	0.7296	[0,0.103]	Optimal

n is the total number of subjects

n1 is the number of subjects accrued during stage 1

r1, if r1 or fewer responses are observed during stage 1, the trial is stopped early for futility

r2, if r2 or fewer responses are observed by the end of stage two, then no further investigation of the drug is warranted

EN0 is the expected sample size for the trial when response rate is p0

Interval for w is the set of values w such that the design minimizes w * n + (1 – w) * EN0

11.2 Statistical Analysis:

Primary objective of efficacy or activity:

All patients who received ≥1 dose of durvalumab + cetuximab will be assessed for efficacy and the endpoints of efficacy will be defined as primary end points in this study. For the primary end point- ORR, the frequency or the rate will be estimated from the data and an exact (or binomial) test will be performed to test the sample rate against the null rate (14%). For outcomes of CR, PR, SD and PD rates, descriptive statistics, in particular the frequency (in %) will be summarized.

Kaplan-Meier (K-M) curves will be used to summarize censored secondary endpoints of PFS, OS, and Duration of Response. Medians of time to event will be estimated from K-M curves.

Secondary objective of safety or AEs:

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. The primary end point of Grade ≥3 AE rate will be summarized using frequency in % and tested against the null rate (of 53%) using an exact (or binomial) test. Other secondary AE rates will be summarized using frequency in %.

In the event, that the efficacy endpoint excludes the null rate of 14% (the ORR is higher) but the safety endpoint null rate of 53% is included, then the safety endpoint would take precedence and the combination at the dosing tested would be considered unsafe.

Secondary endpoints of immunoregulatory activity

This will be summarized using frequency in % if they are categorical and mean ± std or median (range) if they are numerical respectively. Endpoints will be assessed of relations or associations using regression models, ANOVA models and logistical models respectively to accommodate numerical and categorical types of dependent and independent variables (i.e. endpoints).

12 ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice (GCP).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

12.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator will have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects.

12.3 Informed consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Subjects unable to give their written consent (e.g., stroke or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

13 DATA MANAGEMENT

13.1 Data Storage

Data collection and storage will be managed by the University of Cincinnati Cancer Center, Clinical Trials Office (UCCC CTO). The UCCC CTO will maintain storage of all clinical data in accordance with federal guidelines and GCP. Data will be entered in a secure, password protected storage database, REDCap. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team.

13.2 Data and Safety Monitoring

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients.

The internal UCCC Data Safety Monitoring Board (DSMB) will monitor the progress of this study. The DSMB is an independent group of experts who will advise the study investigators and report relevant findings to IRB or other appropriate authorities.

This study will be evaluated at least twice a year by the DSMB or at a frequency determined to be necessary by the committee. The DSMB will focus on the analytic plan to include: hypothesis, primary objective, endpoints and will monitor study conduct including accrual, protocol required tests, IND, toxicities and efficacy. The DSMB will review data provided by the study team with respect to accrual, and AEs or other information pertinent to evaluate the continuing safe conduct of this study. All meetings and determinations are recorded by the DSMB Coordinator.

DSMB initial study evaluation will occur after previous Protocol Review and Monitoring committee (PRMC) and Institutional Review Board (IRB) approval. If the DSMB recommends a study design amendment or the PI desires to amend the study, PRMC approval will be required.

14 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

14.1 Identity of investigational product(s)

Table 10. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune
Cetuximab	*100 mg/50 mL (50 mL); 200 mg/100 mL (100 mL)*	Eli Lilly and Company

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Appendix 1. Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy (TMG Version 17NOV2020)

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also, other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and non-immune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in this protocol – whether that is MEDI4736 alone, tremelimumab alone, or MEDI4736 + tremelimumab in combination, or MEDI4736 +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to Protocol, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the CTCAE version specified in the clinical study protocol.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 17 November 2020

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.
Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for IVIG and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed 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. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	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** – 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.
	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. • 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	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV

		completion of steroid taper.	methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with study physician, as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the	**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

CTC grade/severity)		(such as sepsis, peritoneal signs, and ileus). – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist,consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary

	• 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.	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 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressants such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. [a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.
Grade 3 or 4	**Grade 3** • For patient treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 2 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 2 days, continue steroids and promptly add further immunosuppressants (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating

		discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1	• No dose modifications. • If it worsens, then treat as Grade 2.	**For Grade 1** – Continue LFT monitoring per protocol.
	Grade 2	• Hold study drug/study regimen dose until	**For Grade 2** – Regular and frequent checking of LFTs (e.g., every 1 to 2

		Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	days) until LFT elevations improve or resolve. – If no resolution to Grade ≤1 in 1 to 2 days, consider discussing with study physician, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
Grade 3 or 4	**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 Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.

		• For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. **For Grade 4** Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg. – For HCV+ patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with HBcAb+: Evaluate for both HBV and HCV as above.
	Isolated AST or ALT >ULN and ≤5.0×ULN,	• No dose modifications. • If ALT/AST elevations represents significant worsening based on	

	whether normal or elevated at baseline	investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN . • If toxicity worsens, then treat as described for elevations in the rows below.If toxicity improves to AST or ALT ≤5.0×ULN , resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressants (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology

			consult).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with study physician, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressant (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):			

- **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise**
- **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)**
- **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**

Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consult a 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, decreased urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
	Grade 1	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	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 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, consider additional workup.When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – 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, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol 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). – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY**

Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emolient, lotion, or institutional standard).
Grade 2	For persistent (>1 week) 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.
Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. • If toxicity worsens, then treat as Grade 4.	**For Grade 3 or 4** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with study physician.

		For Grade 4 Permanently discontinue study drug/study regimen.	
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with study physician, as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c).If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.

Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2, 3, or 4	• For Grade 2-4 endocrinopathies other than hypothyroidism and type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve. • Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper. • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 diabetes mellitus (DM) may be treated

		study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement. • If toxicity worsens, then treat based on severity.	with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Consider Gastroenterology referral

	Grade 1	No dose modifications.	**For Grade 1** – IV hydration – Manage as per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2** Hold study drug/study regimen dose until resolution to Grade ≤1. **For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**

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. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. • If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE).
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.

Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**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 (e.g., 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 (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. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and

		followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2** – Consider discussing with the study physician, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., 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. o Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with study physician, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. *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.

- 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.
- Avoid medications that can worsen myasthenia gravis.

GUILLAIN-BARRE:

- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
- Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the study physician, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac

		biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4	• If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the

		discontinue study drug/study regimen. • If Grade 3-4, permanently discontinue study drug/study regimen.	discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional

			laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1	• No dose modifications.		**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.		**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving

		input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3 or 4	**For Grade 3** • Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4** • Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult – Consider discussing with the study physician, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label**

	for general guidance before using infliximab.
	– Consider whether patient may require IV IG, plasmapheresis.

[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.
[c]NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

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; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • 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. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

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.

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	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 (e.g., 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 (e.g., 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 (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, 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 (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs 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.
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.

Appendix 2. Durvalumab dose calculations

For Durvalumab dosing done depending on patient weight (patients ≤ 30kg):

1. Cohort dose: X mg/kg

2. Patient weight: Y kg

3. Dose for patient: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is Durvalumab nominal concentration.

The corresponding volume of Durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

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

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

Example:

1. Cohort dose: 20 mg/kg

2. Patient weight: 30 kg

3. Dose for patient: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 600 mg/50 (mg/mL) = 12.0 mL

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

Number of vials = 12.0 (mL)/10.0 (mL/vial) = 2 vials