Protocol Date: July 31, 2023

Official Title of Study: A Phase I Trial of MR-Guided Dose-Escalated Hypofractionated Adaptive Radiation Therapy and Immunotherapy in Primary Metastatic or Very Locally Advanced Patients With Head and Neck Cancer

NCT04477759

MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

A Phase I Study of MR-Guided Dose-Escalated Hypofractionated Adaptive Radiation Therapy and Atezolizumab in Primary Metastatic, Locally Advanced and Locally Recurrent Patients with Head and Neck Cancer

Short Title:

DEHART Study

Musaddiq Awan, MD (Study PI)

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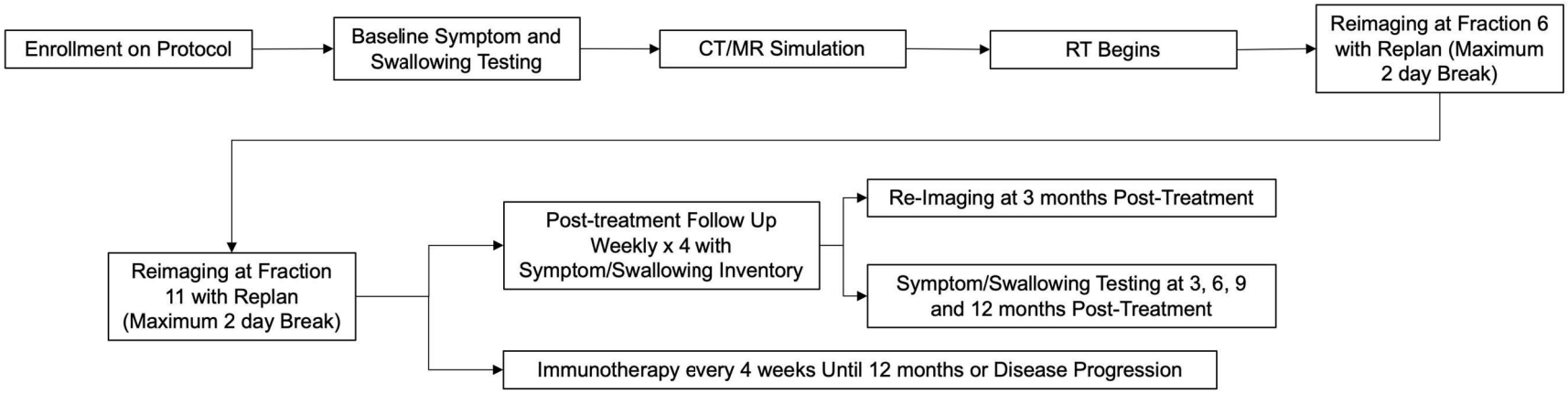
PROTOCOL SUMMARY

Title	A Phase I Study of MR-Guided Dose-Escalated Hypofractionated Adaptive Radiation Therapy and Atezolizumab in Primary Metastatic, Locally Advanced and Locally Recurrent Patients with Head and Neck Cancer
IND Sponsor	Sponsor-Investigator
Principal Investigator	Musaddiq Awan, MD
Clinical Trial Phase	I
Study Population	Locally Advanced Patients with Head and Neck Cancer
Primary Objectives	To determine the maximum-tolerated dose (MTD) of the DEHART regimen delivered with adjuvant atezolizumab in patients with locally advanced or *de novo* metastatic HNSCCs.
Secondary Objectives	1. To evaluate the efficacy of the DEHART regimen at one year as measured by locoregional control and overall survival. 2. To assess gross tumor shrinkage after six and 11 fractions of radiotherapy using the DEHART regimen. 3. To assess patient quality of life during and after the DEHART regimen as measured using multiple patient quality-of-life metrics.
Study Design	We propose a pilot phase I study using a Time-to-Event Continual Reassessment (TITE-CRM) design to estimate the MTD. Locally advanced (defined as T3-T4NanyM0 or T1-T4 N1-N3M0 or locoregionally recurrent after surgery) and *de novo* metastatic HNSCC patients with no prior history of head and neck radiation and a life expectancy of at least 12 months will be enrolled. Baseline symptom evaluation will be obtained using validated surveys of head and neck cancer patients: the MD Anderson Symptom Inventory for Head and Neck (MDASI-HN) and the MD Anderson Dysphagia Inventory for Head and Neck (MDADI-HN). Patients will then undergo treatment using DEHART and adjuvant atezolizumab and will then be followed for up to one year.

Number of Subjects	18
Estimated Time to Complete Enrollment:	Approximately two years

STUDY SCHEMA



STUDY CALENDAR

Study Assessment	Screening[1]	Pre-Treatment SLP Eval[2]	Radiotherapy Simulation[2]	RT Fx 1	RT Fx 2 -4	RT Fx 5	RT Fx 6-9	RT Fx 10	RT Fx 11	RT Fx 12 - 14	RT Fx 15	1 wk Post-RT Follow-Up[3] (+/- 3 days)	2, 3 and 4 wk Post-RT Follow-Up[3] (+/- 3 days)	Immuno-therapy Visits Post RT (q28d + 7 days)	3 mo Post-RT Follow-Up[3] (+/- 14 days)	6 mo Post-RT Follow-Up (+/- 14 days)	9 and 12 mo Post-RT Follow-up[3] (+/- 14 days)
				Scheduled as per institutional guidelines													
Radiation Oncologist Visit	X			X (One visit prior to initiaton of fraction 6)			X (One visit prior to initiation of fraction 11)		X (One visit no later than 24h after fraction 15)			X	X		X	X	X
Medical Oncologist Visit	X											X		X			
Cisplatin Eligibility Evaluation	X																
AE reporting		Recorded until completion of the 12 month follow-up period															
Concomitant Medications		Recorded from signing of the ICF through 30 days after the last dose of study drug															
CBC with Diff	X													X			
CMP[4]	X													X			
TSH, T3,T4	X													X			
Amylase/Lipase	X																
PT/INR	X																
Pregnancy Test[5]	X																

Study Assessment	Screening[1]	Pre-Treatment SLP Eval[2]	Radiotherapy Simulation[2]	RT Fx 1	RT Fx 2 -4	RT Fx 5	RT Fx 6-9	RT Fx 10	RT Fx 11	RT Fx 12 - 14	RT Fx 15	1 wk Post-RT Follow-Up[3] (+/- 3 days)	2, 3 and 4 wk Post-RT Follow-Up[3] (+/- 3 days)	Immuno-therapy Visits Post RT (q28d + 7 days)	3 mo Post-RT Follow-Up[3] (+/- 14 days)	6 mo Post-RT Follow-Up (+/- 14 days)	9 and 12 mo Post-RT Follow-up[3] (+/- 14 days)
				Scheduled as per institutional guidelines													
HIV and hepatitis B surface antigen (HBsAg)	X																
CT Chest or PET/CT to assess for distant metastatic disease	X																
CT Simulation			X														
MR simulation including Anaotmic/Functional Acquisitions			X														
Radiotherapy				X	X	X	X	X	X	X	X						
Anatomic/Functional MR Acquisitions			X	X	X	X	X	X	X	X	X						
DCE MRI (optional)						X		X			X						
Radiation Planning			X				X		X								
Atezolizumab 1680 mg IV														X			
Research Biopsy (optional)			X			X					X						
SLP Evaluation		X													X	X	
VFSS Study		X													X	X	
FOIS Score		X													X	X	
DIGEST Grade		X													X	X	
MDASI-HN Survey			X			X (+/-		X (+/-			X (+/-	X	X		X	X	X

Study Assessment	Screening[1]	Pre-Treatment SLP Eval[2]	Radiotherapy Simulation[2]	RT Fx 1	RT Fx 2 -4	RT Fx 5	RT Fx 6-9	RT Fx 10	RT Fx 11	RT Fx 12 - 14	RT Fx 15	1 wk Post-RT Follow-Up[3] (+/- 3 days)	2, 3 and 4 wk Post-RT Follow-Up[3] (+/- 3 days)	Immuno-therapy Visits Post RT (q28d + 7 days)	3 mo Post-RT Follow-Up[3] (+/- 14 days)	6 mo Post-RT Follow-Up (+/- 14 days)	9 and 12 mo Post-RT Follow-up[3] (+/- 14 days)
				Scheduled as per institutional guidelines													
						48 hrs)		48 hrs)			48 hrs)						
MDADI Survey			X			X (+/- 48h)		X (+/- 48h)			X (+/- 48 hrs)	X	X		X	X	X
EAT-10 Questionnaire		X													X	X	
PET/CT															X		
Diagnostic Neck MRI															X		

1. All screening procedures must occur within 30 days prior to enrollment.
2. Should be comepletd before starting radiation treatment
3. If a subject has disease progression/relapse, then they will be followed for treatment-related toxicity up to 1-year, subject withdrawal or death as per follow-up requirements.
4. Including alkaline phosphatase, ALT/AST, total bilirubin, total protein, albumin, calcium, phosphorus, magnesium, creatinine, glucose, potassium, sodium, chloride, bicarbonate AND uric acid
5. For women of childbearing potential. A negative pregnancy test (serum) must be obtained within 30 days prior to the first study intervention.

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Cell (Count)
CQ	Chloroquine
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DCE	Dynamic Contrast Enhancement
DEHART	Dose-Escalated Hypofractionated Adaptive Radiotherapy
DFS	Disease-Free Survival
DLT	Dose-Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HNSCCs	Head and Neck Squamous Cell Carcinomas
IP	Investigational Product
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MCWCC	Medical College of Wisconsin Cancer Center
MRgRT	MR-guided Radiation Therapy
MTD	Maximum-Tolerated Dose
NCI	National Cancer Institute
NSCLCs	Non-small cell lung cancers

ORR	Overall Response Rate
PD-L1	Programmed Cell Death Ligand-1
PR	Partial Response
RT	Radiation Therapy
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease
SD	Standard Deviation
SRC	Scientific Review Committee
TITE-CRM	Time-to-Event Continual Reassessment
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others

1 BACKGROUND

1.1 Introduction

Locoregional failure remains the principle mode of mortality in head and neck squamous cell carcinomas (HNSCCs) treated with conventional chemoradiation therapy over seven weeks. Radiation dose escalation with hypofractionation has shown unparalleled local control in many other malignancies, such as non-small cell lung cancer, but has been stymied in HNSCCs due to toxicity concerns. MR-guided radiation therapy (MRgRT) allows for adaptive radiation dose escalation based on tumor response, which may improve therapeutic outcomes while limiting toxicities.

Our protocol, titled Dose-Escalated Hypofractionated Adaptive Radiotherapy (DEHART), evaluates a novel framework for radiation delivery using MRgRT with atezolizumab in patients with advanced HNSCCs. Unlike conventional radiotherapy, DEHART modifies the radiation dose using MRgRT by adapting the radiation plan weekly during the course of treatment, escalating radiation dose to residual tumor while deescalating radiation dose to areas of tumor regression. We hypothesize that DEHART will safely deliver ablative radiation doses in 15 fractions over three weeks while limiting both toxicity and the effect of tumor repopulation by resistant clonogens, thus resulting in an improved therapeutic ratio.

We aim to test this hypothesis through a phase I clinical trial with the following specific aims: (1) Determine the maximum-tolerated dose (MTD) of the DEHART regimen delivered using MRgRT with adjuvant atezolizumab in a population of patients who are not candidates or unsuitable for definitive chemoradiation therapy; (2) Evaluate the toxicity and functional outcomes of the DEHART regimen including changes in baseline speech, swallow and quality of life; and (3) Assess the efficacy of DEHART and obtain volumetric and functional imaging correlates of efficacy using MRgRT to serve as hypothesis-generating data for future trials of radiation dose adaptation. To determine the MTD of the DEHART regimen, we propose an 18 patient study using a modified Time-to-Event Continual Reassessment (TITE-CRM) phase I design with three radiation dose levels delivered to regressing disease: 50 Gy in 15 fractions, 55 Gy in 15 fractions and 60 Gy in 15 fractions.

If DEHART is found to be safe and shows a signal of efficacy in this study, we will conduct a future phase II trial to compare this novel treatment strategy to standard-of-care conventionally fractionated chemoradiation in patients with locally advanced HNSCCs.

1.2 Study Significance and Rationale

Hypofractionated Radiation Has Shown Excellent Outcomes for Local Control in Many Malignancies: Locoregional failure remains the principle cause of mortality in patients with head and neck squamous cell carcinomas (HNSCCs). In many other malignancies, short course, high dose per fraction radiation therapy (RT), referred to as hypofractionated RT, has been shown to provide excellent local control. For example, using a technique called stereotactic body radiation therapy (SBRT), a total dose of 50-54 Gy in 3-5 fractions can be delivered in 1-1.5 weeks for early-stage non-small cell lung cancers (NSCLCs), resulting in local control upward of 90%. (1) Despite such advances in other malignancies, the use of SBRT in HNSCCs has been limited to the re-irradiation setting in which a second course of RT is delivered to a field that received a prior full-dose course of RT. This limited use is due to multiple reasons including toxicity concerns of using SBRT in the definitive setting, an inability to safely treat microscopic regional nodal disease with SBRT, and concerns regarding the efficacy of SBRT at the established HNSCC re-irradiation

dose of 40 Gy in 5 fractions. In fact, in the phase II trial establishing this SBRT dose in the re-irradiation setting, local progression-free survival (PFS) was only 60% with one-year locoregional PFS only approaching 37%. (2) Though this modest number accounts for the high mortality rates and radioresistance associated with a retreated population, this SBRT regimen is likely insufficient for the long-term local control needed in *de novo* treatment of HNSCCs.

Another hypofractionated regimen that has been used in NSCLC with local control comparable to SBRT (approaching 90%) is 60 Gy in 15 fractions. **(3) We find this regimen appealing to establish in HNSCCs for three reasons: 1) It may be delivered in only three weeks; 2) Using the linear-quadratic model to compare RT dose regimens (11), it is equivalent to a 2 Gy per fraction dose (EQD2) of 70 Gy, which is the conventional RT dose for gross disease for locally advanced HNSCCs; and 3) It easily allows for integrated treatment of areas at risk for microscopic regional disease spread using a safe dose of 40 Gy in 15 fractions (EQD2 of 42.2 Gy).** Further, by delivering this equivalent dose over three weeks, there is limited ability for tumor repopulation by relatively radioresistant clonogens, resulting in a greater likelihood of tumor control compared to conventional RT based upon first principles.

MR-Guided Adaptive Radiation Therapy May Allow for Safe Hypofractionation in HNSCCs: Prior attempts at hypofractionation in HNSCCs have been stymied due to concerns regarding acute and late toxicities of radiation as well as the known benefit of radiosensitizing cisplatin. In particular, phase I-II trials of SBRT treating small volumes for early stage laryngeal cancers have shown moderate to high rates of laryngeal edema and laryngeal necrosis. (4-6) Further, laryngeal and/or hypopharyngeal involvement in the reirradiation SBRT experience was associated with a 50% rate of Grade 3+ late toxicities. (7)

In these studies, radiation has typically been given in a non-adaptive fashion, with a single dose given to the entire area of gross disease involvement prior to the beginning of therapy without modification due to tumor shrinkage. Adaptive RT allows for replanning of radiation based on tumor shrinkage. Previously, the ability to perform adaptive RT has been hampered by poor quality daily anatomic and functional treatment imaging using cone-beam CT and the lack of a framework to rapidly replan patients without a repeat CT simulation. Recently, the development of magnetic resonance-guided radiation therapy (MRgRT) has allowed for improved image guidance and high-quality acquisition of anatomic and functional imaging daily during RT. (8) In anticipation of daily dose adaptation, MRgRT has been developed with rapid plan adaptation in mind and a new radiation plan using MRgRT may be obtained in a matter of minutes to hours compared to many days for a. typical CT plan. Thus, MRgRT may improve locoregional outcomes in patients with HNSCCs by facilitating safe hypofractionation through anatomic and functional imaging response-based radiation dose adaptation. We are uniquely positioned at our institution to deliver adaptive RT as we have an MRI-guided linear accelerator, allowing for high-quality imaging of gross disease as it visibly regresses during RT. Using our MRI-guided linear accelerator, **we have observed that during conventionally fractionated RT, rapid regression of HNSCCs may be appreciated on MR-guided imaging during the first weeks of treatment.** Given this, **we propose using adapted MR-guided RT (MRgRT) to allow for safe delivery of the dose-escalated hypofractionated regimen of 60 Gy in 15 fractions in HNSCCs**.

Locoregional Control Remains Critically Important in Locally Advanced and Metastatic HNSCCs and in Poor Performance Status Patients. Standard management of the primary disease site in patients with primary metastatic HNSCC is not well defined, even though failure to control local and regional disease remains the number one cause of morbidity and mortality in this population. Additionally, unresectable disease and locally recurrent disease after surgery, is

best managed by a clinical trial, per NCCN guidelines. The principle recommendation for primary metastatic disease according to NCCN guidelines is to consider locoregional treatment and then pursue systemic therapy.

Despite advances in radiotherapy and chemotherapy delivery, standard-of-care management for locally advanced HNSCCs remains concurrent chemoradiation therapy with cisplatin over seven weeks of treatment. However, in the case of primary metastatic disease or poor performance status patients, this seven-week course significantly delays initiation of systemic therapy. Furthermore, it is uncertain whether the side effects associated with chemoradiation, including a severe toxicity rate as high as 50%, (9) are justified in these settings of limited life expectancy. This has led to variable practice in the management of locoregional disease in these patients: some physicians choose to perform upfront concurrent chemoradiation as in the non-metastatic setting; some utilize palliative radiotherapy approaches without chemotherapy; (10) while others omit upfront radiotherapy altogether in order to proceed immediately to primary systemic immunotherapy or chemoimmunotherapy. (11-13)

However, recent data show that despite having primary metastatic disease, very locally advanced disease or even poor performance status, HNSCC patients still have a modest life expectancy and may be suitable for locoregional treatment and enrollment on a phase I trial. The KEYNOTE-048 trial reported that the median survival of metastatic patients with PD-L1 immunotherapy exceeds one year (13 months). (13) Additionally, Al-Mamgani et al. (14) report the effectiveness of hypofractionated radiation using 50 Gy in 16 fractions (median survival 17 months) in patients not suitable for curative treatment despite including 9% *de novo* metastatic patients (the typical *de novo* metastatic rate for HNSCCs) and 16% poor performance status patients. **Given the variable management of this group of patients and the importance of addressing locoregional disease in this population, locally advanced patients, primary metastatic patients and poor performance status patients are an excellent patient population to test the safety of our novel hypofractionated RT paradigm prior to testing this in a more curative population.**

Immunotherapy and Radiation Have Shown Synergy in Preclinical Models: The rationale for combining radiation with immunotherapy stems from preclinical evidence of a synergistic antitumor effect of both treatment modalities on cancer cells. Studies have shown that radiation therapy may induce both innate and adaptive anti-tumor immune response.by modulating the host's immune system, and making tumor cells more susceptible to T-cell-mediated attack. (15) In particular, radiation promotes the release of tumor neoantigens from dying tumor cells which enhances MHC class I expression and upregulates chemokines, cell-adhesion molecules, and other immunomodulatory cell surface molecules, ultimately triggering an antitumor immune response and leads to immunogenic cell death. (16) Further, investigators have shown that the expression of programmed cell death ligand-1 (PD-L1), a checkpoint activated by tumor cells to evade the immune system, is upregulated in response to radiation in preclinical models of multiple tumor subtypes. (17, 18) **As such there is increased interest in combining PD-1/PD-L1 immunotherapy to increase the efficacy of both modalities.**

PD/1-PD-L1-targeted Immunotherapy Is Safely Delivered with Radiation Therapy and Has Shown Promising Outcomes in Very Advanced and Metastatic HNSCCs and Is Being Tested in the Primary Setting. Multiple clinical trials have established the role of primary PD-1/PD-L1-targeted immunotherapy in locally advanced, recurrent, and metastatic HNSCCs. (11-13) Checkmate 141 (19) established the role of nivolumab in the second-line setting and compared nivolumab with the investigator's choice of standard-of-care (SOC) therapy (weekly cetuximab, docetaxel, or methotrexate) for platinum-refractory disease demonstrating a significant and durable overall survival (OS) advantage for nivolumab 7.7 months versus 5.1

months (HR = 0.68, 95%CI: 0.54-0.86). Similarly, the pembrolizumab-based KEYNOTE-012 (20) and KEYNOTE-055 trials (21) showed the efficacy of pembrolizumab in cisplatin-refractory and cisplatin- and cetuximab-refractory HNSCC. Additionally, pembrolizumab alone and with combination chemotherapy (5-FU and cisplatin) has shown improved overall survival in the first-line setting for treatment of recurrent and metastatic HNSCC in the KEYNOTE-048 (13) study when compared to the prior standard of care EXTREME regimen (platinum, 5-FU and cetuximab).

More recently, one of these PD-1/PD-L1-targeted agents, atezolizumab, has shown efficacy and safety in patients with heavily pretreated HNSCCs, potentially suggesting high levels of efficacy in the upfront setting. (22). In this study, 21 patients (66%) experienced a treatment-related adverse event (TRAE), with three experiencing grade 3 TRAEs and one experiencing a grade 4 TRAE (per CTCAE. No grade 5 TRAEs were reported. This TRAE rate of atezolizumab of 66% in this study is favorably comparable to the grade 3+ TRAE rate of 55% reported by pembrolizumab in KEYNOTE-048. Further, the grade 3+ TRAE rate of 12.5% is much lower than that of pembrolizumab on KEYNOTE-048. Objective responses to atezolizumab by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) occurred in 22% of patients, with a median duration of response of 7.4 months (range 2.8-45.8 months), which is comparable to the any response rate of 17% on KEYNOTE-048 (13). Median progression-free survival with atezolizumab was 2.6 months (range 0.5-48.4 months), and median overall survival was 6.0 months (range 0.5-51.6+ months) in a heavily pretreated population.

Given that PD-1/PD-L1-targeted agents have also been safely delivered with definitive radiation therapy in patients with non-metastatic HNSCCs (23, 24) and the known efficacy of atezolizumab, **we propose testing our novel RT regimen with adjuvant atezolizumab in this population, providing excellent local therapy without significantly delaying effective systemic therapy for these patients.**

1.3 Study Innovation

DEHART is a novel framework for delivering RT. The DEHART concept is depicted in Figure 1 utilizing image data from a patient treated using MRgRT. The image on the left demonstrates the initial gross disease burden highlighted in pink (including both the base of tongue primary and left level 2 lymph node), the area of subclinical microscopic disease spread highlighted in green and the area of elective nodal treatment highlighted in blue. The image on the right is a mid-treatment image of the same patient, with the residual gross disease highlighted in pink. Classically, the pink area would receive the highest dose of radiation, the green area would receive an intermediate dose of radiation and the blue area the lowest therapeutic radiation dose to account for the relative amount of potential disease in these areas. In conventional fractionation, this would typically include a dose of 70 Gy in 35 fractions (EQD2 of 70 Gy) to the pink area, 60-63 Gy in 35 fractions (EQD2 of 58.55-61.95 Gy) to the green area, and 54-56 Gy in 35 fractions (EQD2 of 51.93-54.13 Gy) to the green area. Using DEHART, the pink area would receive a dose of up to 60 Gy in 15 fractions (EQD2 of 70 Gy), the green area would receive a dose of 45 Gy in 15 fractions (EQD2 of 48.75 Gy) and the blue area would receive a dose of 40 Gy in 15 fractions (EQD2 of 42.2 Gy). Though the relative EQD2 of the intermediate and low dose areas is smaller than conventional fractionation, the shorter treatment time (less than half the overall treatment time) should make the effective dose similar.

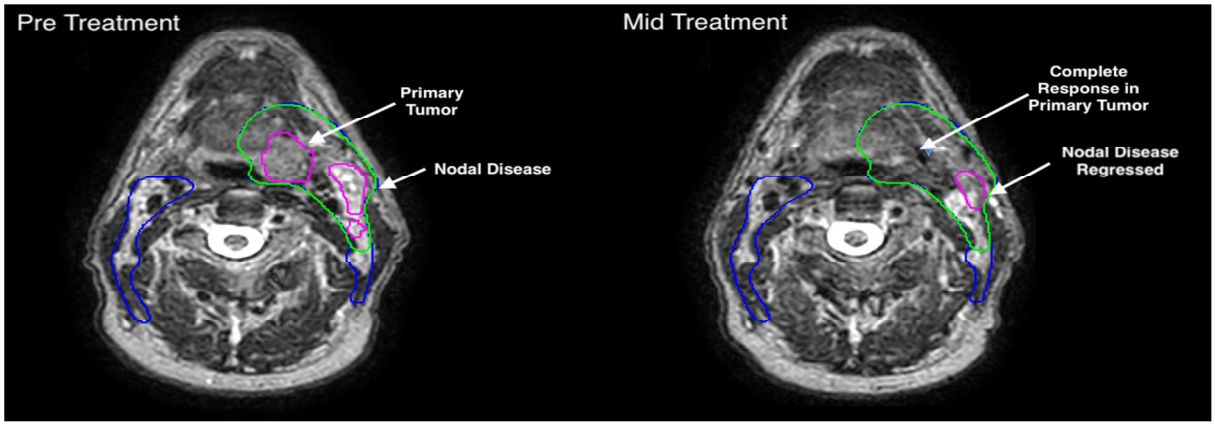


Figure 1 DEHART Adapts Radiation Based on Tumor Response. ***Radiation targets volumes for a patient treated using DEHART are depicted both pretreatment (left) and mid-treatment (right): the pink outlines gross disease which receives the highest dose of radiation, the green outlines subclinical spread which receives an intermediate dose of radiation, and the blue outlines microscopic nodal disease which receives an even lower dose of radiation. In conventional radiotherapy, target volumes and doses are defined pre-treatment (left) and remain constant. DEHART adapts the pink volume weekly during treatment as tumor regresses, (right) allowing for safe radiation dose escalation by dynamically reducing the volume receiving the highest radiation dose to the slowest-responding areas.***

In addition to the difference in dose and fractionation, the second facet of the DEHART regimen is changing target volumes. Using the current treatment paradigm, the pink volume would not change throughout treatment and would receive the same uniform dose regardless of tumor regression during treatment. **DEHART would reduce dose to the area that has regressed (no longer depicted in pink in the image on the right)** to the intermediate radiation dose received by the green volume **while maintaining the same radiation dose to the residual pink volume.** This would allow for safe hypofractionation by sparing toxicity to responding tissues.

2 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

We hypothesize that dose-escalated hypofractionated adaptive radiation therapy (DEHART) to 60 Gy in 15 fractions is safe and tolerable with adjuvant atezolizumab for locoregional disease in HNSCC patients. To test this, we propose a phase I radiation dose-escalation trial with adjuvantt atezolizumab in a population of HNSCCs not suitable for conventional seven-week chemoradiation (including locally advanced and *de novo* metastatic patients). This allows us to establish the safety of this regimen in patients for whom locoregional therapy is critical. If safe and demonstrates a signal of efficacy, this phase I trial will serve as a foundation for future trials comparing DEHART with atezolizumab to standard-of-care chemoradiation.

2.1 Primary Objectives

To determine the maximum-tolerated dose (MTD) of the DEHART regimen delivered with adjuvant atezolizumab in patients with locally advanced or *de novo* metastatic HNSCCs.

2.2 Secondary Objectives

1. To evaluate the efficacy of the DEHART regimen at one year, as measured by locoregional control and overall survival.
2. To assess gross tumor shrinkage after six and eleven fractions of radiotherapy using the DEHART regimen.
3. To assess patient quality of life during and after the DEHART regimen as measured using multiple patient quality-of-life metrics.

2.3 Primary Endpoint

The primary endpoint of the study is to determine the MTD of the DEHART regimen delivered with adjuvant atezolizumab, as determined using a modified TITE-CRM Methodology.

2.4 Secondary Endpoint(s)

1. One-year locoregional control of patients receiving DEHART (efficacy objective).
2. One-year overall survival of patients receiving DEHART (efficacy objective).
3. Median and mean percent tumor shrinkage at fractions six and 11 of radiotherapy (tumor shrinkage objective).
4. Tumor shrinkage by RECIST criteria at fractions six and 11 of radiotherapy (tumor shrinkage objective).
5. Temporal changes in the CTCAE version 5.0 scores (quality-of-life objective).
6. Temporal changes in composite MDASI-HN scores, composite MDADI scores, EAT-10 questionnaire scores, Functional Oral Intake (FOIS) scores and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) grading (quality-of-life objective).
7. Temporal changes in quantitative MR parameters including DCE in patients undergoing the DEHART regimen.
8. Genomic and transcriptomic changes during treatment with the DEHART regimen.

3 STUDY DESIGN

3.1 General Description

We propose a pilot phase I study using a Time-to-Event Continual Reassessment (TITE-CRM) design to estimate the MTD. Locally advanced (defined as T3-T4NanyM0 or T1-T4 N1-N3M0 or locoregionally recurrent after surgery) and *de novo* metastatic HNSCC patients with no prior history of head and neck radiation and a life expectancy of at least 12 months will be enrolled. Baseline symptom evaluation will be obtained using validated surveys of head and neck cancer patients: the MD Anderson Symptom Inventory for Head and Neck (MDASI-HN) (25) and the MD Anderson Dysphagia Inventory for Head and Neck (MDADI-HN). (26) Patients will then undergo treatment using DEHART and adjuvant atezolizumab and will then be followed for up to one year.

Cumulative radiation dose to the gross disease is the experimental agent in this study, which will be the subject of dose escalation. The MTD will be determined as the radiation dose at which there is a 30% rate of dose-limiting toxicity (DLT) up to one year after treatment (to allow for the development of late toxicities from radiation).

All patients will receive a 15-fraction course of radiation therapy to the primary disease and regional nodes, including an elective nodal field using an adaptive image-guided approach.

Radiation will be delivered to the elective neck to a total dose of 40 Gy in 15 fractions, to a 1-cm anatomically confined margin on initial gross disease to 45 Gy in 15 fractions and to the experimental dose in 15 fractions to gross disease (50 Gy, 55 Gy or 60 Gy) with shrinking volumes after every five fractions based on tumor response during therapy. All patients will receive adapted MR-guided therapy with replanning prior to the delivery of fraction 6 and fraction 11 of radiotherapy.

Patients will undergo standard consultation to receive head and neck radiotherapy for HNSCC and will be determined to be eligible for the clinical trial. If eligible, patients will receive informed consent about the risks and benefits of the trial and if they accept, will sign confirming their enrollment. Additional consent will be obtained for research-specific biopsies and dynamic contrast MRI acquisitions. If availale, initial diagnostic biopsy specimens (obtained at the time of cancer diagnosis prior to enrollment) will be tested for baseline PD-L1 expression/Combined Positive Score per standard testing in anatomic pathology. Patients will then undergo standard radiotherapy simulation, including CT simulation with and without IV contrast and MRI simulation with and without Gadolinium contrast. Patients will complete baseline MDASI-HN and MDADI surveys. Patients will also be followed with a speech and language pathologist (SLP) and undergo videofluoroscopic swallow studies (VFSS) prior to treatment, three months after treatment and six months after treatment, as is standard of care in the treatment of HNSCCs. At baseline and follow-up SLP evaluations, patients will also complete the EAT-10 questionnaire and the SLP will compute both the Functional Oral Intake Scale (FOIS) score and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) grade. On the day of CT and MR simulation, patients who provided optional additional consent will undergo a research biopsy for histologic, genomic and RNA analysis.

A radiation treatment plan will be developed as per the proposed DEHART regimen: the PTV_High (gross disease plus 3-mm setup margin) will receive the experimental dose in 15 fractions, the PTV_Intermediate (a 1-cm anatomically confined margin on the gross disease plus 3-mm setup margin) will receive a dose of 45 Gy in 15 fractions and the PTV_Low (elective lymph node regions plus 3-mm setup margin) will receive a dose of 40 Gy in 15 fractions.

Patients will then undergo daily MR-guided radiotherapy on a Monday to Friday basis for a total of 15 fractions. MR images will be acquired detailing anatomic and functional data on a daily basis. On the day of the six and 11th fractions, MR imaging will be acquired for replanning. A new gross tumor volume will be segmented on the MR imaging by the treating physician, and a new PTV_High volume will be developed. Anatomically confined changes resulting from weight loss or tumor shrinkage will be made to the PTV Intermediate and PTV_Low volumes if necessary. An adaptive replan will be made to be delivered to begin on the current fraction for the next five fractions.

During each fraction of MR-guided radiotherapy, MR imaging will be obtained for the patients including volumetric T1 and/or T2-weighted sequences for tumor visualization, quantitative T1 maps, quantitative T2 maps and intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) maps. Additionally, patients who provide additional consent will undergo dynamic contrast enhancement (DCE) MR imaging on the day of fractions 5, 10 and 15, which would require IV placement and contrast injection. As these patients will receive daily MR-guided radiation treatment, we do not anticipate any missing MRI acquisitions.

During treatment, all patients will be evaluated for acute toxicities at least once every five fractions with a physician visit. Additionally, patients will complete repeat MDASI-HN and MDADI surveys on the day of treatment review.

After completion of the DEHART regimen, patients will receive atezolizumab 1680 mg every four weeks up to one year after completion of radiotherapy. Patients will be seen in follow-up at the following time points after completion of radiotherapy: weekly for the first four weeks, at three months, six months, nine months and 12 months. Patients will complete repeat MDASI-HN and MDADI surveys to assess for quality-of-life outcomes at each follow-up. Repeat imaging, including a PET/CT and diagnostic MRI of the head and neck, will be ordered at the three-month follow-up. The diagnostic MRI will assess for anatomic response at the primary site and lymph nodes and the PET/CT will be to assess for both locoregional response to treatment and distant staging. Based on data from PET-NECK, (27) PET obviates the need for salvage neck dissection in patients with PET-negative residual lymph node tissue after definitive radiation. Further, PET could determine if there is disease progression outside the head and neck.

To assess efficacy of the DEHART regimen, evaluation of locoregional control and overall survival will be made by the treating radiation oncologist at each follow-up. Patients will be followed for disease control until locoregional progression, completion of the 12-month follow-up period, patient refusal or death.

In order to understand the acute and long-term toxicities of the DEHART regimen, patients will be followed clinically by the treating radiation oncologist, undergo routine MDASI-HN and MDADI surveys, and undergo scheduled SLP visits, including VFSS, EAT-10 questionnaires, FOIS scoring and DIGEST grading, as detailed in the prior section. For the purposes of this study, acute toxicity will be deemed any toxicity that occurs within 90 days of completion of radiation therapy, and late toxicity will be deemed any toxicity that occurs more than 90 days after completion of radiation therapy. During each weekly treatment review and each post-treatment follow-up, the treating physician will record a pain score (scale 1 to 10) and use the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) to record toxicity scores for dysphagia, oral mucositis, dehydration and weight loss. The treating physician will also record tracheostomy tube dependence and feeding tube dependence at each visit.

3.2 Study Completion

The study will reach study completion approximately 24 months from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
- Screening: period after consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibly criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- On follow-up: from last day of treatment to the end of follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local principal investigator.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent, but are not subsequently assigned to the study intervention or enrolled in the study. MCWCC CTO will follow its SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Screening Procedures

Refer to study calendar of events.

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

4.5 Eligibility Confirmation

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.
No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the MCW PI can only provide guidance or clarification on eligibility. Any eligibility questions should be directed to Musaddiq Awan, MD (mawan@mcw.edu).

Inclusion Criteria

1. Patients 18 years or older with AJCC 8th edition T3-T4 N0-N3 M0 or T0-T4 N1-N3 M0 squamous cell carcinoma of the head and neck squamous cell carcinoma of the larynx, hypopharynx, oropharynx, oral cavity, or carcinoma of unknown head/neck primary) with measurable disease who meet **at least** one of the following three criteria:
    a) **Not** candidates for concurrent bolus cisplatin-based chemoradiation therapy, as deemed by a medical oncologist. To ensure patients meet this criteria, investigators should complete the online tool at comogram.org prior to registration to determine if the patient is eligible. Examples of contraindications to cisplatin include but are not limited to:
        - Age ≥ 70 with moderate to severe comorbidity or vulnerability to cisplatin, defined as having one or more of the following conditions within four week of registration:
            - Modified Charlson Comorbidity Index ≥ 1.
            - ACE-27 Index ≥ 1.
            - ω score < 0.80.
            - G-8 score ≤ 14.
            - CARG Toxicity Score ≥ 30%.
            - CIRS-G Score ≥ 4.
        - Age < 70 with severe comorbidity or vulnerability to cisplatin, defined as having two or more of the following conditions within four weeks prior to registration
          Modified Charlson Comorbidity Index ≥ 1.
            - ACE-27 Index ≥ 1.
            - ω score < 0.80.
            - G-8 score ≤ 14.
            - CARG Toxicity Score ≥ 30%.
            - CIRS-G Score ≥ 4.
        - Creatinine clearance < 60 cc/min by the Cockroft-Gault formula.
        - Preexisting peripheral neuropathy.
        - Clinical need for a hearing aid or 25+ decibel shift over two contiguous frequencies on a pretreatment hearing test.
    b) **Refuse** concurrent cisplatin-based chemoradiation therapy.
    c) Have **recurrent disease after definitive surgical resection or an unresected oral cavity cancer (for which primary surgery is considered standard of care)**

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Investigator/Enrolling Physician Initials: _____ Date: _____

2. **Or any patient** 18 years or older with primary metastatic (AJCC 8th edition T1-T4 N0-N3 M1) squamous cell carcinoma of the head and neck.
3. Zubrod performance status 0–3.
4. Measurable primary and/or nodal tumor in the head and neck region at the time of radiotherapy.
5. Patients must have the psychological ability and general health that permits completion of the study requirements and required follow-up.
6. Ability to tolerate multiple MRIs.
7. Adequate hematologic function within 14 days prior to registration defined as follows: Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3, platelets ≥ 100,000 cells/mm^3, hemoglobin ≥ 9.0 g/dl, lymphocyte count ≥*500/mL.* (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable). Adequate hepatic function within 14 days prior to registration defined as follows: AST or ALT ≤ 2.5 times institutional upper limit of normal, serum bilirubin ≤ 1.5 x institutional upper limit of normal.
   For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN
   - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
8. Negative HIV test at screening, with the following exception: patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200/μL, and have an undetectable viral load}.
9. Negative hepatitis B surface antigen (HBsAg) test at screening
10. Inclusion of Covid-19 positive patients will be based on standard institutional protocol.
11. Female patients must meet one of the following:
    - Postmenopausal for at least one year before the screening visit, or
    - Surgically sterile (i.e., undergone a hysterectomy or bilateral oophorectomy), or
    - If subject is of childbearing potential (defined as not satisfying either of the above two criteria), agree to practice two acceptable methods of contraception (combination methods require use of two of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male or female condom, hormonal contraceptive) from the time of signing of the informed consent form through 150 days after the last dose of study agent, AND
      - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptom-thermal, post ovulation methods] and withdrawal are not acceptable contraception methods).
12. Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to one of the following:
    - Practice effective barrier contraception during the entire study period and through 150 calendar days after the last dose of study agent, OR
    - Must also adhere to the guidelines of any study-specific pregnancy prevention program, if applicable, OR
      - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptom-thermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
13. Ability to understand a written informed consent document, and the willingness to sign it.

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Investigator/Enrolling Physician Initials: _____ Date: _____

Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Prior invasive malignancy within the past three years (except for non-melanomatous skin cancer, and early-stage treated prostate cancer);
2. Life expectancy less than 12 months
3. Performance status Zubrod >3.
4. Inability to encompass all gross disease in 19 cm superior to inferior planning target volume to be treated on the MR-linac.
5. MRI-incompatible foreign body.
6. Claustrophobia precluding ability to tolerate multiple MRIs.
7. MRI-incompatible pacemaker or ICD placement.
8. Patients with cochlear implant.
9. Patients with prior radiation therapy to the head and neck Note: Prior external beam radiotherapy is excluded, but Iodine 131 is allowed.
10. Prior systemic therapy, including cytotoxic chemotherapy, biologic/targeted therapy, or immune therapy for the study cancer.
11. Major surgery within 28 days prior to registration.
12. Body weight ≤ 30 kg.
13. Any of the following severe laboratory abnormalities within 14 days of registration, unless corrected prior to it: sodium < 130 mmol/L or > 155 mmol/L; potassium < 3.5 mmol/L or > 6 mmol/L; glucose < 40 mg/dl or > 400 mg/dl; serum calcium (ionized or adjusted for albumin) < 7 mg/dl or > 12.5 mg/dl; magnesium < 0.9 mg/dl or > 3 mg/dl.
14. Unstable angina and/or congestive heart failure requiring hospitalization within three months prior to step 1 registration.
15. Transmural myocardial infarction within three months prior to step 1 registration.
16. Respiratory illness requiring hospitalization at the time of step 1 registration.
    Note: If the respiratory illness is resolved and the patient meets the eligibility status above, then the patient can be considered for the trial.
17. Idiopathic pulmonary fibrosis or other severe interstitial lung disease that requires oxygen therapy or is thought to require oxygen therapy within one year prior to step 1 registration.
18. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
19. Clinically apparent jaundice and/or known coagulation defects.
20. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], 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 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 five years may be included but only after consultation with the medical oncology study chair; patients with celiac disease controlled by diet alone.

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21. History of active primary immunodeficiency including, but not limited to Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition. The need to exclude patients with AIDS from this protocol is necessary because the treatment involved in this protocol may be immunosuppressive.
22. Current or prior use of immunosuppressive medication within 14 days before registration, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
    Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Principal Investigator confirmation has been obtained. Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
23. Receipt of live attenuated vaccination within 30 days prior to registration.
24. Medical or psychiatric illness which would compromise the patient's ability to tolerate treatment or limit compliance with study requirements.
25. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during treatment and for five months after the last dose of atezolizumab, this exclusion is necessary because the treatment involved in this study may be significantly teratogenic. Women who are breastfeeding are also excluded.
26. Prior allergic reaction or hypersensitivity to atezolizumab or any of study drug excipients.
27. History of allogenic stem cell or organ transplantation.
28. Uncontrolled hypertension.
29. Uncontrolled cardiac arrhythmia.
30. Uncontrolled serious chronic gastrointestinal condition associated with diarrhea.
31. 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. 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.
32. History of leptomeningeal disease
    Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
33. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
    Patients with indwelling catheters (e.g., PleurXâ) are allowed.
34. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)

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Investigator/Enrolling Physician Initials: _____ Date: _____

35. Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis:
    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover < 10% of body surface area
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
36. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
37. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
38. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
    - Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

    Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
39. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
40. Live, attenuated vaccines (e.g., FluMistâ) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
41. Current treatment with anti-viral therapy for HBV
42. Treatment with investigational therapy within 28 days prior to initiation of study treatment
43. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
44. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
45. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
46. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
47. Known allergy or hypersensitivity to any component of the chemotherapy formulation

CRC Initials: _____ Date: _____

Investigator/Enrolling Physician Initials: _____ Date: _____

48. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment
49. Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible."

_____ _____

(CRC Signature) (Date)

_____ _____

(Investigator/Enrolling Physician Signature) (Date)

4.6 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol, and AEs/SAEs will continue to be reported according to this protocol.

In the absence of treatment delays due to adverse events, study treatment/intervention may continue until:

- Disease progression.
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- Inter-current illness that prevents further treatment administration.
- Subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
- Study stopping rules are met.

Subjects who sign the informed consent form, enroll and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCWCC CTO will follow their IRB of record's SOPs regarding consent withdrawal.

If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal, with no study follow-up.
- Selective consent withdrawal from interventional portion of the study but agrees to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.7 Lost to Follow-up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered, **AND**
    - A letter (Appendix 2) to the participant's last known mailing address goes unanswered, **AND**
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore® (Follow-up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the study team, the subject should be considered in follow-up again.

4.8 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® tracks accrual throughout the study.
- If the study must be suspended, OnCore® is updated to a "suspended' status."
- When the accrual number is reached, OnCore® notifies staff of study closure.

4.9 End of Study Definition

A participant is considered to have completed the study if he or she completed all phases of the study, including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

4.10 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study PI, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB), and the sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 TREATMENT PLAN

5.1 Radiation Therapy

Radiation therapy will be delivered using MR-guided radiation on a 1.5 T high-field MR-linac using intensity-modulated radaition therapy.

5.1.1 Simulation, Localization and Treatment Planning Requirements

Patients must be immobilized using a thermoplastic head mask extending to include neck and shoulder immobilization.
Treatment planning CT and MR images will be required for target volume delineation including gross tumor volume (GTVs), clinical target volumes (CTVs) and planning target volumes (PTVs). CT will be used for dose calculation. All tissues to be irradiated should be included in the CT and MR scan. CT and MR slice thickness should be 2 mm or less
Treatment planning will be performed so the patient may receive treatment on the 1.5 T high-field MR-linac. A backup plan will be generated in case of technical issues to be delivered on a conventional linear accelerator.

5.1.2 Target Volumes

MRI images will be segmented by the attending radiation oncologist to define the target volumes detailed below:

GTVp: The initial GTVp is defined as all known gross disease determined from clinical information, endoscopic examination, MRI and PET images. This will be modified at each weekly replan (fraction 6 and fraction 11 of radiotherapy) based on clinical information and MRI images on the day of the replan.
GTVn: The GTVn is defined as all suspicious lymph nodes for disease as determined from clinical information, CT, MRI and PET images. This will be modified at each weekly replan (fraction 6 and fraction 11 of radiotherapy) based on clinical information and MRI images on the day of the replan.
CTV_High: The high-dose CTV will be the union of the GTVp and GTVn contours.
CTV_Int: The intermediate-dose CTV will be a 1-cm anatomically confined margin on the initial GTVp and GTVn defined on the treatment planning scan. This will not be modified on replanning scans except due to anatomic confinement (i.e., due to shrinkage of a level 2 lymph node that displaced the sternocleidomastoid muscle without muscle invasion, the CTV_Int on the replanning scan should not extend to include muscle)
CTV_Low: The low-dose CTV will include any involved lymph node levels and elective lymph node radiation based upon the guidelines outlined in Biau et al. (Biau Green Journal 2019). The CTV low may be truncated inferiorly to ensure that the entire treatment field may be encompassed in a 19-cm superior-inferior volume.
Planning Target Volumes: A margin no larger than 3 mm will be added to the CTV_High, CTV_Int and CTV _Low to define the PTV_High, PTV_Int and PTV_Low, respectively for daily changes in setup motion.

5.1.3 Critical Normal Tissues

Required critical normal tissues to be segmented (recommended labeling in italics) include:

- Brainstem (Brainstem).
- Spinal Cord (SpinalCord).
- Brainstem PRV 5 mm (Brainstem_PRV03).
- Spinal Cord PRV 5 mm (SpinalCord_PRV05).
- Left (OpticNrv_L) and right (OpticNrv_R) optic nerves.
- Optic chiasm (OpticChiasm).
- Mandible (Bone_Mandible).
- Left (Parotid_L) and right (Parotid_R) parotid glands.
- Left (Glnd_Submand_L) and right (Glnd_Submand_R) submandibular glands.
- Oral cavity (Oral_Cavity).
- Lips (Lips).
- Supraglottic and glottic larynx (LarynxGSL).
- Pharyngeal constrictors (Pharynx).
- Trachea (Trachea).
- Esophagus on Slices with the PTV (Esophagus_S).
- Left (BrachialPlexus_L) and right (BrachialPlexus_R) brachial plexus.
- Patient (Patient).

5.1.4 Radiation Treatment Planning

The treatment plan will be based on the analysis of the volumetric dose, including dose volume histogram analyses of the PTVs and critical normal tissues. Adaptive IMRT planning is mandatory. Patients will undergo radiation re-planning prior to delivery of the sixth and 11^{th} fractions.

5.1.4.1 Dose Fractionation

Once-daily radiation will be given for 15 fractions. The PTV_High will receive the experimental dose ($D_{experimental}$) delivered over 15 fractions (3.33 Gy per fraction at the 50 Gy dose level, 3.66 Gy per fraction at the 55 Gy dose level and 4.0 Gy per fraction at the 60 Gy dose level); the PTV_Int will receive a cumulative dose of 45 Gy over 15 fractions (3.0 Gy / fraction); and the PTV_Low will receive a cumulative dose of 40 Gy over 15 fractions (2.66 Gy/fraction). Due to the adaptive scheme of the protocol, the volume receiving the experimental dose (PTV_High) may decrease after fractions 6 and 11 based on response to treatment. In the case of a rapid complete response, there may be no PTV_High volume.

5.1.4.2 Dose Specification

The prescribed dose for each PTV volume should cover at least 95% of the volume. Additionally, 98% of the prescribed dose for each PTV volume should cover at least 98% of the volume.
As an acceptable deviation, 95% of the prescribed dose for each PTV volume should cover at least 95% of the volume. Additionally, 93% of the prescribe dose for each PTV volume should cover at least 98% of the volume.

5.1.4.3 Dose Constraints

Required

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV_High	$D_{95\%}$ $D_{98\%}$	$D_{experimental}$ 98% of $D_{experimental}$	95% of $D_{experimental}$ 93% of $D_{experimental}$
PTV_Int	$D_{95\%}$ $D_{98\%}$	45 Gy 44.1 Gy	42.75 Gy 41.85 Gy
PTV_Low	$D_{95\%}$ $D_{98\%}$	40 Gy 39.2 Gy	38 Gy 37.2
Patient	$D_{0.03cc}$	106% $D_{experimental}$	110% $D_{experimental}$
Spinal Cord	$D_{0.03cc}$	30 Gy	37.5 Gy
Brainstem	$D_{0.03cc}$	30 Gy	37.5 Gy
SpinalCord_PRV05	$D_{0.03cc}$	37.5 Gy	45 Gy
Brainstem_PRV03	$D_{0.03cc}$	37.5 Gy	45 Gy
OpticNrv_L or OpticNr	$D_{0.03cc}$	30 Gy	37.5 Gy
OpticChiasm	$D_{0.03cc}$	30 Gy	37.5 Gy
Mandible	$D_{0.03cc}$	45 Gy	108% $D_{experimental}$
Esophagus	$D_{0.03cc}$	45 Gy	108% $D_{experimental}$
Trachea	$D_{0.03cc}$	45 Gy	108% $D_{experimental}$
BrachialPlexus_L or BrachialPlexus_R	$D_{0.03cc}$	40 Gy	$D_{experimental}$

Recommended

Structure	Dosimetric Parameter	Recommended Constraint
Mandible	$V_{30\ Gy}$ $V_{40\ Gy}$	< 50% < 33%
Parotid_L or Parotid_R	D_{mean}	22 Gy
Glnd_Submand_L or Glnd_Submand_R	D_{mean}	33 Gy
Pharynx	D_{mean}	37.5 Gy
LarynxGSL	D_{mean}	37.5 Gy
Lips	$D_{0.03cc}$	30 Gy
Oral Cavity	D_{mean}	25 Gy
Esophagus	D_{mean}	30 Gy

5.1.5 Treatment Verification

Daily CBCT or MRI is required for treatment setup.

5.1.6 Daily Anatomic and Functional Imaging

During each fraction of radiation therapy, anatomic and functional imaging maps will be obtained during treatment setup and delivery. The following imaging sequences will be acquired:

- Volumetric T1 and/or T2-weighted imaging for tumor visualization.
- Quantitative T1 maps.
- Quantitative T2 maps.
- Intravoxel Incoherent Motion Diffusion-Weighted Imaging (IVIM-DWI).

Additionally, if a patient provides additional consent, DCE-MRI will be obtained on the day of fraction 5, fraction 10 and fraction 15 of radiotherapy.

Functional imaging will be anonymized and stored on research servers with unique identifiers to correlate functional images to treatment outcomes for a secondary analysis of tumor-related response.

5.2 Systemic Therapy

Following completion of radiotherapy, atezolizumab 1680 mg will be administered every 28 to 35 days beginning no earlier than 28 days after the first fraction of radiotherapy. There will be a minimum gap of 28 days between doses of atezolizumab initiated after completion of radiotherapy. Atezolizumab will continue to be administered up to a total of 12 doses. The last dose of atezolizumab will be no later than 365 days after the first fraction of radiotherapy and may be discontinued at the discretion of the medical oncologist due to toxicity or disease progression.

5.2.1 Drug Administration and Patient Assessment during Systemic Therapy

After completing radiation, atezolizumab 1680mg will be administered every 28 days for up to a total of 12 doses or until 365 days after initiation of radiation treatment. Routine blood work including a CBC, CMP and TSH with reflex T4 will be done with each atezolizumab administration. A provider and lab visit will be added to all treatment days.

During the first dose of atezolizumab, no premedication will be given prior to infusion. Vital signs (heart rate, respiratory rate, blood pressure and temperature) will be measured within 60 minutes prior to infusion. Atezolizumab will be infused over 60 (+/- 5) minutes. If clinically indicated, vital signs should be measured every 15 (+/-5) minutes during infusion and at 30 (+/-10) minutes after the infusion. Patients will be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms.

During subsequent atezolizumab infusions, atezolizumab should be administered over 30 (+/- 10) minutes if previous infusions were tolerated without infusion reaction and 60 minutes (+/- 10) minutes if the patient experienced an infusion reaction to atezolizumab previously. Premedication

with antihistamines, antipyretics and/or analgesics may be administered for patients who previously experienced an infusion-related reaction to atezolizumab.

A history and physical examination should be performed at study screening and prior to the first dose of atezolizumab. This history and physical should include pertinent medical history (including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures)), reproductive status and social history. All medications including prescription drugs, over-the-counter medications, vaccines, herbal/homeopathic remedies and nutritional supplements used within seven days prior to beginning therapy with atezolizumab will be recorded. A complete physical examination should include vital signs, evaluation of the head, eyes, ears, nose, and throat, cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurologic symptoms. Any abnormality identified at baseline should be recorded on the general medical history and baseline conditions eCRF.
Prior to each subsequent dose of atezolizumab, an interval medical history should be obtained including changes in medications and allergies and symptom-directed physical examinations including vital signs should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities will be recorded. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Physical examinations should include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

5.3 Atezolizumab Dose Management and Modifications

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit versis risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be rechallenged with atezolizumab only after approval has been documented by the study investigator.

5.3.1 Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1: Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [C,d] • For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact study investigator. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over one month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., almost 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by study investigator.

[b] If corticosteroids have been initiated, they must be tapered over one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be rechallenged with atezolizumab only after approval has been documented by study investigator.

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

5.3.2 Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2. Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug. For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2: Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test; ULN = upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 10-mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be on the investigator's benefit risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over one month to 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

5.3.3 Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for more than seven days. • Monitor closely.

Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist around five days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact study investigator. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over one month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10-mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

5.3.4 Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms, such as headache, fatigue, myalgias, impotence, constipation or mental status changes, should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4: Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab. [c]

Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve, and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the

investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

5.3.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact study investigator. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to grade 1 or better, taper corticosteroids over one month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10-mg/day oral prednisone. The acceptable length of the extended period of time must be on the investigator's benefit risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit risk assessment and documented by the investigator.

5.3.6 Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in **Error! Reference source not found.**. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 Immune-mediated pericardial disorders, Grades 2□4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

5.3.7 INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in **Error! Reference source not found.**.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	● Immediately interrupt infusion. ● Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. ● In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ● For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Grade 2[a] Fever[b] with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	● Immediately interrupt atezolizumab infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus as needed. ● Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the sponsor-investigator.

Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	● Permanently discontinue atezolizumab.[f] ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	● Permanently discontinue atezolizumab.[f] ● Administer symptomatic treatment.[c] ● Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator. ● Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab according to institutional guidelines and the above table. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after considering the benefit-risk ratio.
g. Refer to Riegler et al. [61] for information on experimental treatments for CRS.

5.3.8 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10-mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c] • For recurrent events, permanently discontinue atezolizumab and contact study investigator. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c] • For recurrent events, permanently discontinue

	atezolizumab and contact study investigator. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact study investigator. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over one month.

GI = gastrointestinal; ULN = upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10-mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the study investigator.

[b] If corticosteroids have been initiated, they must be tapered over one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit risk assessment and documented by the investigator.

5.3.9 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9: Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10-mg/day oral prednisone, increasing dose to 1–2 mg/kg/day, if event does not improve within 48–72 hours. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact study investigator. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above.

	If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10-mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon the study investigator.[b] If corticosteroids have been initiated, they must be tapered over one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit risk assessment and documented by the investigator.

5.3.10 Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10: Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For facial paresis: – If event resolves fully, resume atezolizumab [b] • If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10-mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the study investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ one month to the equivalent of ≤ 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit risk assessment and documented by the investigator.

Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

5.3.11 Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11: Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact study investigator. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over one month.

5.3.12 Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies(including prerenal and postrenal causes, and concomitant medications such asnon-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12: Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c]

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact study investigator. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10-mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit risk assessment and documented by the investigator.

5.3.13 Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13: Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Immune- mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Study investigator. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact study investigator. [c]
Immune- mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact study investigator. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Study investigator. [c] • For recurrent events, treat as a grade 4 event.

Immune- mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact study investigator. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over one month.

[a] Atezolizumab may be withheld for a longer period (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10-mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the study investigator.[b] If corticosteroids have been initiated, they must be tapered over one month to the equivalent of 10-mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re challenge patients with atezolizumab should be based on the investigator's benefit risk assessment and documented by the investigator.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100 x 10^9/L (100,000/µL)
  - ANC < 1.0 x 10^9/L (1000/µL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)

- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181 x 10^9/L (181,000/µL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	· Permanently discontinue atezolizumab and contact Medical Monitor. · Consider patient referral to hematologist. · Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. · Consider initiation of IV corticosteroids and/or an immunosuppressive agent. · If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. · If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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5.4 Dietary Restrictions

None.

5.5 Monitoring Subject Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Comprehensive instructions will be provided to the patient in order to ensure compliance with treatment.

5.6 Acquisition of Tumor Specimens

For patients who provide additional consent, tumor biopsies will be performed prior to any treatment on either the day of CT or MR simulation, on the day of the fifth fraction of radiotherapy, on the day of the fifteenth fraction of radiotherapy and at the time of locoregional recurrence (if applicable). Biopsies will be performed in the clinics under local anesthesia. Tumor from each biopsy will be placed in sterile conical tubes filled with prechilled (4°C) CO_2 independent media (Gibco Cat#: 18045-088) supplemented with 1X antibiotic/antimycotic (Gibco #15240-096). These specimens will be immediately transported to Dr. Himburg's laboratory for storage and later analysis. A portion of each biopsy specimen may be cryopreserved for additional future potential *in vitro* multi-omic correlative studies. These biopsies will allow for the evaluation of genomic and transcriptomic changes in the tumor microenvironment resulting from treatment in the DEHART

regimen and markers of therapeutic resistance in the recurrent specimens which may provide data for novel therapeutic avenues to combine with DEHART.

6 ADVERSE EVENTS: DEFINITIONS, COLLECTION AND REPORTING REQUIREMENTS

6.1 Definitions

6.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6).

This includes the following:

- Adverse events not previously observed in the subject that emerge during the protocol-specified adverse event reporting period, including signs or symptoms associated with head and neck cancer that were not present prior to the adverse event reporting period.

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

- If applicable, adverse events that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified adverse event reporting period.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

6.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.

- **Life-threatening**. Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- **Pregnancy**

- **Congenital anomaly/birth defect:** Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

6.1.3 Assessment of Severeity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. The below table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]

4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE v5.0 which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event;" it must be reported as a serious adverse event.

d. Grade 4 and 5 events must be reported as serious adverse events.

6.1.4 Attribution of an Adverse Event

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to atezolizumab (see following guidance), and actions taken.

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

Definitely Related: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably Related: *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly Related: *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Unlikely: *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration

of the trial intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: *The AE is clearly NOT related to the intervention.* The AE is completely independent of study intervention, and/or evidence exists that the event is definitely related to another etiology.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes: Related (definitely, probably, possibly, unlikely)

There is a plausible temporal relationship between the onset of the AE and administration of the atezolizumab and/or radiotherapy and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug or with similar treatments; and/or the AE abates or resolves upon discontinuation of the atezolizumab and/or radiation therapy or dose reduction and, if applicable, reappears upon rechallenge.

No: Not Related (unrelated)

Evidence exists that the AE has an etiology other than the atezolizumab and/or radiation therapy (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab administration (e.g., cancer diagnosed two days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

6.1.5 Expectedness of an Adverse Event

Study investigator or treating physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form and/or drug information brochure. Expected adverse events of atezolizumab are those adverse events that are listed or characterized in the package insert (PI) or current investigator brochure (IB).

Unexpected adverse events of atezolizumab are those not listed in the PI or current IB or not identified that are not attributable to radiotherapy. This includes adverse events for which the specificity or severity is not consistent with the description in the PI. or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described for the study intervention (atezolizumab and/or radiotherapy).

6.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

6.2.1 Collection of Adverse Events

All (or specify if only certain grade AE needed) adverse events (including SAEs) must be recorded in OnCore® and/or an adverse event log. All AEs required to be collected must be graded

according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator's or treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through completion of the entire 12-month follow-up period. After this period, investigators should only report SAEs that are attributed to prior study treatment. AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.
Please see section 6.2.2 and table 14 to identify the adverse events that need to be reported.

6.2.2. Procedures for eliciting, recording, and reporting adverse events

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- ❑ "How have you felt since your last clinical visit?"
- ❑ "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

6.2.2.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

6.2.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

6.2.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be reassessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or

character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

6.2.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

6.2.2.5 Pregnancy

If a female subject becomes pregnant while receiving the study drug or five months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

6.2.2.6 AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the investigator to the sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., regulatory authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy’s law:
- Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical

symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Events of Special Interest specific to atezolizumab are:

- Systemic lupus erythematosus.
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis.
- Nephritis.
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis).
- Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis).
- Vasculitis.
- Autoimmune hemolytic anemia.
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis).
- Myelitis
- Facial paresis

6.2.2.7 Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an adverse event and transmitted to Genentech:

- Data related to the product usage during breastfeeding.
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors).
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

6.2.2.8 Product complaints

A product complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

6.2.2.9 Post-Study Adverse Events

For studies involving extended follow-up period, the investigator after the end of the adverse event reporting period should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study that is believed to be related to prior exposure to study drug.

Case transmission verification will be performed by both parties during this period to ensure successful transmission of single case reports

6.2.3 Reporting of Adverse Events and Serious Adverse Events

Sponsor-investigator will be responsible for collecting all protocol-defined adverse events (AEs)/serious adverse events (SAEs), pregnancy reports, other special situation reports, AESIs and product complaints with an AE where the patient has been exposed to the investigational product

Please refer to table 15 below to identify adverse events that meet reporting requirements.

All serious adverse events (SAEs) must also be documented in OnCore®.

Table 15

<table>
<tr><th rowspan="3">Attribution</th><th colspan="4">SAE</th><th colspan="3">AE</th></tr>
<tr><th colspan="2">Grade 1, 2 & 3</th><th colspan="2">Grade 4 and 5</th><th>Grade 3</th><th colspan="2">Grade 4</th></tr>
<tr><th>Expected</th><th>Unexpected</th><th>Expected</th><th>Unexpected</th><th>Unexpected</th><th>Expected</th><th>Unexpected</th></tr>
<tr><td>Unrelated
Unlikely</td><td rowspan="2">IRB[1] and DSMC[2]-Routine Review[3]</td><td>IRB[1] and DSMC[2]-Routine Review[3]</td><td rowspan="2">IRB[1]-Routine Review[3]
DSMC[2]-Within 5 calendar days</td><td>IRB[1]-Routine Review[3]
DSMC[2]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Routine Review[3]</td><td rowspan="2">DSMC[2]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Within 5 calendar days</td></tr>
<tr><td>Possible
Probable
Definite</td><td>IRB[1] and DSMC[2]-Within 5 calendar days
FDA[4]</td><td>IRB[1] and DSMC[2]-Within 5 calendar days
FDA[4]</td></tr>
</table>

1. Guidance on adverse event reporting to the IRB is available online at MCW IRB Policies and Procedures.
2. For expedited DSMC reporting, study coordinator/research nurse must notify the DSMC via email including the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. DSMC will review data entered into OnCore®.
3. For routine reporting, the events will be reported to IRB as part of the annual continuing progress report and the DSMC will review data entered into OnCore® at the time of scheduled monitoring.
4. Fatal or life-threatening SAEs meeting the criteria indicated in the above table will be reported to FDA no later than seven calendar days after study staff's initial awareness of the event. If the SAE is not fatal or life-threatening and meets the above criteria, the timeline for submitting an IND safety report to FDA is no later than 15 calendar days after study staff's initial awareness of the event. See section 6.2.3 for detailed reporting instructions.

6.2.3.1 Exchange of Single Case Reports with Genentech

All protocol-defined adverse events (AEs)/serious adverse events (SAEs), pregnancy reports, other special situation reports, AESIs and product complaints with an AE where the patient has been exposed to the product must be reported to Genentech. The Council for International Organizations of Medical Sciences (CIOMS) forms should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All product complaints without an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	30 calendar days of the awareness date
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	30 calendar days of the awareness date.
AESIs	30 calendar days of the awareness date.

- Serious Adverse Drug Reactions (SADRs)

Serious AE reports that are related to the product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within 30 calendar days of the awareness date.

- Other SAEs

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within 30 calendar days of the awareness date.

- Special Situation Reports
    - Pregnancy reports
      While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the product, shall be transmitted to Genentech within 30 calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

    - Other special situation reports, as defined above, shall be transmitted to Genentech within 30 calendar days of the awareness date.

- Product Complaints

All product complaints (with or without an AE) shall be forwarded to Genentech within 30 calendar days of the awareness date.

- AESIs

AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within 30 calendar days

6.2.3.2. Case Transmission Verification of Single-Case Reports

The sponsor agrees to conduct the case transmission verification to ensure that all single-case reports have been adequately received by Genentech via sponsor-investigator emailing Genentech a quarterly line-listing documenting single case reports sent by sponsor-investigator to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the ‘Activation Package.’

Following case transmission verification, single-case reports which have not been received by Genentech shall be forwarded by sponsor-investigator to Genentech within five calendar days from request by Genentech.

At the end of the study, a final cumulative case transmission verification report will be sent to Genentech.

6.2.4 Reporting Instructions

- **Reporting to Regulatory Authorities, Ethics Committees and Investigators**

  Sponsor investigator, as the sponsor of the study, will be responsible for the expedited reporting of safety reports originating from the study to the regulatory authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

  Sponsor investigator, as the sponsor of the study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

  Sponsor investigator will be responsible for the expedited reporting of safety reports originating from the study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

  Sponsor investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

- **Food and Drug Administration**

  An IND safety report will be submitted for any adverse event that meets all three definitions: possibly related to the study drug, unexpected, and serious. If the adverse event does not meet one of the above definitions, it should not be submitted as an expedited IND safety report.

  7 Calendar Day Telephone or Fax Report

  The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of atezolizumab. An unexpected adverse event is one that is not already described in the atezolizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

  15 Calendar Day Written Report

  The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of atezolizumab. An unexpected adverse event is one that is not already described in the atezolizumab investigator brochure.

  Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.
  Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Suggested Reporting Form:

US FDA MedWatch 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

6.2.4.1 Aggregate Reports

All IND annual reports submitted to the FDA by the sponsor-investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

6.2.4.2 Other Reports

Sponsor-investigator will forward a copy of the final study report to Genentech upon completion of the study.

6.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

6.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

A product complaint is a verbal, written or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the drug manufacturer and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a drug manufacturer representative. Product complaints in and of themselves are not reportable events. If a product complaint results in an SAE, an SAE form should be completed.

6.5 Study Close-Out

Any study report submitted to the FDA by the sponsor-investigator should be copied to Genentech. This includes all IND annual reports and the clinical study report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned clinical operations contact for the study:

Atezolizumab IIS Clinical Operations: anti-pdl-1-mpd3280a-gsur@gene.com
And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

6.6 Queries

Queries related to the study will be answered by sponsor-investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the parties. The parties agree that Genentech shall have the final say and control over safety queries relating to the product. Sponsor-investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the product independently but shall redirect such queries to Genentech.

Both parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

6.7 Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the product is used, or where there is media involvement, the party where the crisis originates will contact the other Party as soon as possible.

The parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the product. Sponsor-investigator agrees that it shall not answer such queries from media and other sources relating to the product but shall redirect such queries to Genentech.

6.8 Compliance With Pharmacovigilance Agreement / Audit

The parties shall follow their own procedures for adherence to AE reporting timelines.

Each party shall monitor and, as applicable, request feedback from the other party regarding AE report timeliness in accordance with its own procedures. The parties agree to provide written responses in a timely manner to inquiries from the other party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this agreement, both parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this agreement, the parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant party to solve the non-compliance issues and inform the other party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than 60 calendar days, an audit under the provisions of this agreement can be requested by either party. The parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting party will bear the cost of the audit.

7 PHARMACEUTICAL INFORMATION

Atezolizumab

7.1 Product description

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (PMID: 26970723). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated. Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Atezolizumab is approved in approximately 90 countries for one or more of the following indications: non small cell lung cancer (NSCLC), extensive-stage small-cell lung cancer, hepatocellular carcinoma and alveolar soft part sarcoma.

Atezolizumab targets programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the

magnitude and quality of the tumor-specific T cell response through increased T cell priming, expansion, and/or effector function.

7.2 Physical, Chemical, Pharmaceutical Properties and Clinical Formulation of Atezolizumab

For intravenous administration, atezolizumab is provided in 20-mL (Formulation 1200mg every 3 week), and 15-mL (Formulation 840 mg every 2week) glass vials. All Formulations are in a solution containing histidine acetate, sucrose, and polysorbate 20.

7.3 Pharmacology

Pharmacokinetics and pharmacodynamics data of Atezolizumab have been analyzed from the following atezolizumab monotherapy studies: PCD4989g (22), J028944 (28), IMvigor210 (29), IMvigor211 (30), BIRCH (31), POPLAR (32), FIR 29775807 (33), and OAK (34).

An analysis of 906 patients (35) from two phase I and one phase II metastatic urothelial cancer studies (PCD4989g (22), J028944 (28), IMvigor210 (29)) were the first to report the clinical pharmacokinetics (PK) and pharmacodynamics (PD) of atezolizumab. Atezolizumab exhibited linear PK over a dose range of 1–20 mg/kg, including the labelled 1,200 mg dose. The clearance, volume of distribution, and terminal half-life estimates from population pharmacokinetic (PopPK) analysis of 0.200 L/day, 6.91 L, and 27 days, respectively, were as expected for an IgG1. The PopPK analysis suggested that steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in the area under the concentration-time curve (AUC), maximum concentration (Cmax), and trough concentration (Cmin) were 1.91, 1.46, and 2.75-fold, respectively, following q3w intravenous (IV) administration of 1200 mg atezolizumab.

Based on an analysis of exposure-safety and exposure-efficacy data, the following factors had no clinically relevant effect: age (21-89 years), body weight, sex, positive ADA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status. The effect of moderate or severe hepatic impairment on the pharmacokinetics of atezolizumab is unknown.

7.4 Assessment of Safety of Atezolizumab

Safety findings of single agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated with a manageable adverse event profile. Currently, no MTD, no DLTs, and no clear dose-related trends in the incidence of adverse events (AEs) have been determined. Among 3178 patients treated with single-agent atezolizumab for whom pooled safety data are available the most commonly reported AEs (around 10%) included fatigue, decreased appetite, nausea, cough, dyspnea, constipation, pyrexia, diarrhea, anemia, back pain, vomiting, asthenia, arthralgia, pruritus, rash, headache, urinary tract infection, and peripheral edema.

Immune-mediated AEs are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs are closely monitored during the atezolizumab clinical program. Immune-mediated AEs associated with atezolizumab include pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis,

meningoencephalitis, myocarditis, nephritis, and myositis. Guidance regarding the management of immune-mediated AEs is provided in Section 5.2.

7.4.1 Safety Plan

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below. Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab and radiation will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Section 5.2.

7.4.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Section 5.2 of the protocol for a detailed description of anticipated safety risks for atezolizumab.

7.4.3 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

7.4.4 Adverse Events of Special Interest (Immediately Reportable to the investigators

For patients receiving active treatment with atezolizumab, adverse events of special interest are required to be reported. Please refer to section 6.2.2.6 for adverse events of special interest for this study.

7.5 Formula

Atezolizumab is a fully humanized IgG1 isotype antibody against the programmed cell death-ligand 1 (PD-L1). Atezolizumab is a commercially available drug and will be supplied at no cost by Genentech, Inc.

7.6 Supply

Atezolizumab is a commercially available drug and will be supplied at no cost by the manufacturer Genentech, Inc.

7.7 Physical and Chemical Properties

Late Phase I/II, Phase III, and Commercial Material	
Generic name	Atezolizumab
Chemical name	Humanized monoclonal antibody based on a human IgG1 framework containing heavy chain V_HIII and light chain V□I subgroup sequences.
Chemical structure	The recombinant antibody consists of two heavy chains and two light chains with inter and intra chain disulfide bonds that are typical of IgG1 antibodies.
Molecular weight	150 KD
Description	Colorless to slightly yellow solution

Atezolizumab lacks the N-linked oligosaccharides typically observed on other CHO-derived monoclonal antibodies because it incorporates an amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of each heavy chain, resulting in a non-glycosylated antibody. This non-glycosylated antibody has minimal binding to Fcγ receptors and, consequently, prevents Fc-effector function and depletion of cells expressing PD-L1 at expected concentrations in humans.

7.8 Clinical formulation

The manufacture of atezolizumab drug substance consists of cell culture, harvest, and purification. Please find the dose formulations and vial configurations in the table below. Results from a study by Morrissey et Al support the interchangeable use of 840 mg q2w, 1200 mg q3w, and 1680 mg q4w dosing regimens for atezolizumab, as they are anticipated to demonstrate comparable efficacy and safety profiles while offering patients greater flexibility and convenience in their treatment. (36)

	Phase III/ Commercial Drug Product (F03)	Phase III/ Commercial Drug Product (F05)
Administration	Intravenous	Intravenous
Appearance	Colorless-to-slightly-yellow preservative-free clear liquid solution	Colorless-to-slightly-yellow preservative-free clear liquid solution
Concentration of Ateozlizumab	60 mg/mL	60mg/mL

Nominal Atezolizumab Amount per Vial	1200 mg	840 mg
Other Excipients	Histidine acetate buffered at pH 5.8 containing sucrose and polysorbate 20	Histidine acetate buffered at pH 5.8 containing sucrose and polysorbate 20
Primary Packaging	20 mL glass vial	15 mL glass vial
Extractable Volume	20.0 mL	14.0 mL

Atezolizumab drug products must be refrigerated at 2°C-8°C (36°F-46°F) upon receipt until use. Atezolizumab and the diluent vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab Drug Product or the diluent; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light by keeping the vial in the outer carton.

For intravenous administration, atezolizumab in Formulation F03 or F05 will be administered in IV infusion bags containing 0.9% sodium chloride (NaCl) and infusion lines equipped with 0.2 or 0.22 µm in-line filters. The IV bag may be constructed of polyvinyl chloride, polyolefin or polyethylene, the IV infusion line may be constructed of polyvinyl chloride, polyethylene, or polybutadiene and the 0.2 or 0.22 µm in-line filter may be constructed of polyethersulfone or polysulfone. The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab can be diluted to concentrations between 3.2 mg/mL and 16.8 mg/mL in IV bags containing 0.9% NaCl. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. For flat or fixed dosing (e.g., 840 mg, 1200 mg, or 1680 mg) in IV infusion bags, the dose solution may be stored at 2°C-8°C (36°F-46°F) for 24 hours or at ambient temperature ≤ 25°C (77°F) for 8 hours.

8 STATISTICAL CONSIDERATIONS

8.1 Study Design

This is a Phase I dose-escalation trial of radiation dose using a novel radiation treatment regimen called DEHART. The primary objective of the study is to determine the maximum tolerated dose (MTD) of the DEHART regimen using the Time-to-Event Continual Reassessment Methodology (TITE-CRM). The MTD will be determined as the radiation dose at which there is a 30% rate of dose-limiting toxicity (DLT) up to 12 months after completion of radiation treatment (to allow for the development of late toxicities from radiation treatment). There will be three cumulative radiation dose levels to gross disease: 50 Gy in 15 fractions, 55 Gy in 15 fractions and 60 Gy in 15 fractions. The total sample size for this study is 18 patients to be recruited over 12 months.

TITE-CRM is an adaptive Phase I trial design methodology which allows for MTD-finding by weighting the follow-up contribution of previously enrolled patients to the selection of the dose level for each newly enrolled patient. If a patient dies of disease progression without evidence of radiation-related toxicity, they will be censored for toxicity at the time point of last follow-up. Thus,

TITE-CRM allows for dose modification even if patients have not completed the entire follow-up period. At the enrollment of each new patient (beyond three initial patients enrolled after the protocol amendment removing the concurrent atezolizumab dose who start with the lowest dose of 50 Gy), all available follow-up for all patients already on study enrolled after the protocol amendment removing the concurrent dose of atezolizumab, will be used to determine the dose level for the newly enrolled patient based on the TITE-CRM methodology. For example, if three patients are enrolled every two months, by month seven, the first patient who did not receive concurrent atezolizumab (who enrolled in month 1) provides up to 6 months of follow-up whereas the ninth patient who did not receive concurrent atezolizumab (who enrolled in month 6) provides only about 1 month of follow-up. All available follow-up data from the first nine patients who did not receive concurrent atezolizumab will be used by the TITE-CRM model to make a decision on the dose for the tenth patient. Unlike a standard 3+3 design, the TITE-CRM model may maintain the current dose level, increase the dose level or decrease the dose level based on all available follow-up data at the time of enrollment of the tenth patient.

To implement the TITE-CRM model, we will be using the titecrm function from the R package dfcrm. An unconstrained TITE-CRM model potentially allows for rapid early dose escalation from 50 Gy to 60 Gy. To prevent this overly aggressive dose escalation we will require at least 3 sequential patients to be enrolled at 55 Gy before increasing to 60 Gy.

8.2 Objectives and Analysis Plans

8.2.1 Primary Objective and Analysis Plan

The primary objective of the study is to determine the maximum tolerated dose (MTD) of the DEHART regimen delivered with adjuvant atezolizumab in patients with locally advanced or de novo metastatic HNSCCs.

The MTD will be determined as the radiation dose at which there is a 30% rate of dose-limiting toxicity (DLT) up to 12 months after completion of radiation treatment (to allow for the development of late toxicities from radiation treatment) using the TITE-CRM design.

A DLT will be defined for the purposes of this protocol as an inability to complete radiation treatment within 30 days of the start of radiotherapy not deemed to be related to disease progression or unrelated death, unacceptable toxicity within one year of treatment (Grade 4+ toxicity) probably or definitely related to radiation treatment as deemed by the treating physician, or a death within one year of treatment deemed probably or definitely related to treatment. Expected Grade 3 acute toxicities typical of head and neck radiation, acute dermatitis, acute mucositis, feeding tube placement, electrolyte abnormalities, pain requiring narcotic medication and dehydration requiring IV hydration, resolving within 90 days of treatment will **NOT** be considered DLTs. Grade 4+ late toxicities that may be considered a DLT of reirradiation include but are not limited to:

- Chondronecrosis of the laryngeal cartilages
- Laryngeal edema requiring tracheostomy
- Carotid blowout syndrome or other life-threatening vascular bleed
- Aspiration pneumonia requiring ICU admission not related to tumor progression
- Chronic non-healing wound or soft tissue necrosis requiring flap reconstruction
- Brainstem necrosis
- Radiation myelopathy

Grade 1-3 immune-related toxicity from atezolizumab will not be considered a DLT. Additionally, death deemed unrelated to radiation or atezolizumab (such as death due to malignancy or other comorbidity) will not be considered a DLT.
All patients who initiate radiation therapy will be evaluable for the primary endpoint as long as they initiate radiation therapy.

8.2.2 Secondary Objectives

1. To evaluate the efficacy of the DEHART regimen at 1-year as measured by locoregional control and overall survival
    a. To estimate 1-year locoregional recurrence, patients will be followed for locoregional recurrence during the 12-month follow-up period with death as a competing risk using the methodology of Fine and Gray. Cumulative incidence curve will be plotted to describe overtime dynamics of locoregional recurrence.

    b. To estimate 1-year overall survival, the Kaplan-Meier methodology will be used.
2. To assess gross tumor shrinkage after 6 and 11 fractions of radiotherapy using DEHART
    a. Median and mean percent volume of gross tumor shrinkage after 6 and 11 fractions of radiotherapy using the DEHART regimen

    b. Response rate by RECIST criteria at fractions 6 and 11 of radiotherapy

    c. The gross tumor volume as contoured on the pre-treatment, fraction 6 and fraction 11 scans for each individual patient will be plotted using longitudinal plots.
3. To assess patient quality of life during and after the DEHART regimen as measured using multiple patient quality-of-life metrics
    a. Quality of life changes will be determined by measuring the following quality of life/toxicity scores at the endpoints specified in the study calendar: CTCAE version 5.0 scores, composite MDASI-HN scores, composite MDADI scores, EAT-10 questionnaire scores, Functional Oral Intake (FOIS) scores and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) grading.

    b. To determine changes in quality of life and toxicity scores, longitudinal plots of these scores will be used to determine whether these return to baseline or improve after treatment.

8.3 Sample Size Justification

The projected sample size will be 18, and we estimate an accrual rate of 3 patients every 2 months for a total estimated accrual time of 12 months. Patients will be recruited for the study based on whether they are not candidates for full course definitive chemoradiation either due to inability to tolerate cisplatin, locoregionally recurrent disease after surgery, or de novo metastatic disease. Based on our tumor board presentations, we typically have 6 patients who meet these criteria every month, so the proposed study of 18 patients can be easily accomplished within 12 months of opening if we are able to enroll 25% of eligible patients on this trial. We estimate an accrual of 3 study patients every 2 months (1.5 patients per month)

To verify the feasibility of detecting the MTD with this modified TITE-CRM methodology using a sample size of 18, Monte-Carlo simulation studies (1000 resamples each) with various a priori estimates of toxicity at the 3 doses levels were performed. For these simulation studies the following assumptions were made: (1) a constant hazard of observing a DLT through all available follow-up; (2) a median survival of 17 months (based on a similar patient population reported in Al-Mamgani et al. (14)) (constant hazards as well); (3) a study accrual rate of 3 patients every 2 months during first 12 months and (4) toxicity as a function of dose is modeled using a 1-parameter logistic regression. The results of these simulation studies are detailed in the table below.

Assumed 1-year toxicity rates at 50, 55, and 60 Gy	Probability that MTD is declared at 50, 55 and 60 Gy
5%, 15%, **30%**	4.3%, 32.9%, **62.8%**
15%, **30%**, 45%	31.7%, **47.1%**, 21.2%
30%, 45%, 60%	**78.1%**, 18.4%, 3.5%
10%, **30%**, 50%	23.7%, **54.8%**, 21.5%
10%, 20%, **30%**	10.5%, 37.6, **51.9%**

The probability of correctly identifying the MTD depends on the assumed toxicity at each dose level. However, using a wide variety of assumed toxicities at each dose level and a sample size of 18, results in a good probability of detecting the MTD (~50% or more at each assumed toxicity level). Further, the chance of incorrectly selecting a dose level higher than the true MTD is reasonable (~20% or less at each assumed toxicity level).

Due to the amendment removing the concurrent atezolizumab dose and restarting the TITE-CRM, it may be possible that we will only have sufficient funding and drug support to enroll 13 additional patients (though we intend to obtain funding and drug support for a complete set of 18 patients after the removal of the concurrent atezolizumab dose). To ensure that we will still conduct a meaningful study with as few as 13 patients, we ran similar Monte-Carlo simulation studies (1000 resamples each) for a study of only 13 patients. The results of these simulation studies are detailed in the table below and demonstrate that we only *minimally* increase the chance of declaring an MTD higher than the actual MTD with as few as 13 patients:

Assumed 1-year toxicity rates at 50, 55 and 60 Gy	Probability MTD is declared at 50, 55 and 60 Gy
5%, 15%, **30%**	8.3%, 30.1%, **61.3%**
15%, **30%,** 45%	35.3%, **40.4%**, 24.7%
30%, 45%, 60%	**75%**, 20.5%,3.9%
10%, **30%**, 50%	29.4%, **45.3%**, 25.2%
10%, 20%, **30%**	16.8%, 33.8%, **49.8%**

8.4 Study Monitoring, Interim Analyses, and Early Stopping Rules

This is a Phase I clinical trial. Patients will receive continued follow-up during and after treatment up to 12 months after completion of the DEHART regimen. All side effects will be reported and any adverse events will be reported to the IRB as per national and local clinical trial requirements. The project is monitored at all times by the Principal Investigator and/or co-investigators. A physician is present at all exams. The Institutional IRB reviews each project yearly. If at any time during the study, the probability that the MTD is below 50 Gy is greater than 95%, accrual will be

suspended temporarily. Accrual will only resume, if, after further follow-up, this probability is less than 95%.

Adverse Event Reporting: Any adverse event such as unanticipated or severe toxicity from radiation would be reported to the IRB under the guidelines as required by our Institution. Any DLT will be reported to the MCW DSMC within 5 calendar days of the study staff's knowledge of such an event.

8.5 Systemic Treatment Discontinuation

Patients must permanently discontinue atezolizumab if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Patients will return to the clinic for a treatment/surveillance discontinuation visit 30 days after the final dose of study treatment or final visit or telephone contact.

Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Study Discontinuation by PI

The PI has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients. Patient enrollment is unsatisfactory.

9 DATA AND SAFETY MONITORING PLAN (DSMP)

9.1 Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

9.2 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist, and the study biostatistician. While subjects are on study, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings including attendance are documented.

9.3 Quality Assurance

The MCWCC Clinical Trials Office provides ongoing quality assurance audits. This protocol was classified as high risk and will be reviewed internally by the MCW Cancer Center Clinical Trials Office Quality Assurance Staff according to the MCWCC Data and Safety Monitoring Plan and current version SOP, 6.5.2 Internal Quality Assurance Reviews.

9.4 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

9.5 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension, or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

10 REGULATORY COMPLIANCE, ETHICS, AND STUDY MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

10.1 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.2 Pre-study Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

10.3 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be

approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the subject (and Legally Authorized Representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, hospital staff was present for consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients that require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

10.4 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, [and the sponsor(s) and their agents] (include bracketed portion if applicable). This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked Clinical Research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the Case Report Forms contain the study identifiers, subject initials, date of birth and date of service.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor/s or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

10.5 Protection of Human Subjects

10.5.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.5.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

10.5.3 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

10.6 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11 DATA HANDLING AND RECORD KEEPING

11.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss, or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians, and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

11.2 Data Management Responsibilities

Principal Investigator

The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication, and investigational product(s), measurements, exams, evaluations, and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

Research Coordinator
A research coordinator creates, collects, and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

Research Nurse/Medical Staff
The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events, and compliance to study procedures.

Biostatistician
The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

11.3 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

11.4 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document outcomes. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The Clinical Research Coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

11.5 Study Record Retention

The principal investigator is required to maintain adequate records.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial (A Phase I Study of MR-Guided Dose-Escalated Hypofractionated Adaptive Radiation Therapy and Immunotherapy in Primary Metastatic or Very Locally Advanced Patients with Head and Neck Cancer) you participated in.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at
_____

Sincerely,

_____

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