

SUMMARY OF CHANGES – Protocol

For Protocol Amendment: 9

NCI Protocol #: 10405

Local Protocol #: 23-006

NCI Version Date: 09-09-2024

Protocol Date: 09-09-2024

The summary of changes tables below include a detailed summary and rationale for all changes to Protocol #10405 from Protocol Version 11/13/2023 to Protocol Version 09/09/2024.

I. Recommendations following Review of Amendment #8 (received 01/08/2024):

#	Section	Comments
1.	4.1	<i>Please revise the excerpt below as indicated.</i> Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems ~~Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam~~. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability. <u>PI Response:</u> This change has been made.
2.	4.2	<i>Please revise the excerpt below as indicated.</i> An active Federal ~~wide~~ Wide Assurance (FWA) number, <u>PI Response:</u> This change has been made.
3.	4.2.2	<i>Please revise the excerpt below as indicated.</i> Please contact STS Support at Theradex for the training (STS.Support@theradex.com, ~~Theradex phone: 609-799-7580~~). <u>PI Response:</u> This change has been made.
4.	10.3.1	<i>Please revise the excerpt below as indicated.</i> Additional information about the CTEP-AERS integration is available on the

#	Section	Comments
		CTSU members' website: <u>PI Response:</u> This change has been made.

II. Changes made by PI:

#	Section	Change
1.	1.3.1	Baseline tumor ATM expression was changed to baseline tumor ATM mutation status in the exploratory objective.
2.	2.5.1	“ATM expression” was changed to “ATM mutation status” in the Correlative Studies Background to encompass ATM copy number changes, point mutations, insertions, and deletions. ATM expression has been removed as a planned biomarker assay.
3.	5.8	ATM expression was removed from the list of biomarker assays and the priorities of the other biomarkers were updated accordingly.
4.	5.8	Assay laboratory, lab PI, and lab PI contact were updated for WES (tumor), WES (blood), and ctDNA with the following new text: MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov
5.	5.9.1	Section 5.9.1 regarding correlative study to quantify ATM expression was removed as an integrated correlative study.
6.	5.9.1.2- (previously 5.9.2.2)	The site performing WES was updated to the following: WES will be performed at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).
7.	5.9.1.3 (previously 5.9.2.3)	The address for sample shipment from the EET Biobank to site performing WES was updated to the following: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton
8.	5.9.1.4 (previously 5.9.2.4)	Contact information for notification of specimen shipment for WES was updated to the following: Thomas Forbes (mochasamplerereceiving@nih.gov)

#	Section	Change
9.	<u>5.9.2.2-</u> (previously 5.9.3.2)	The site performing ctDNA sequencing was updated to the following: ctDNA sequencing will be performed at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).
10.	<u>5.9.2.3</u> (previously 5.9.3.3)	The address for sample shipment from the EET Biobank to site performing ctDNA sequencing was updated to the following: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton
11.	<u>5.9.2.4</u> (previously 5.9.3.4)	Contact information for notification of specimen shipment for ctDNA sequencing was updated to the following: Thomas Forbes (mochasamplerceiving@nih.gov)
12.	<u>6.6</u>	Duration of follow-up was clarified to indicate that medical record review and/or patient phone call to evaluate toxicity and vitality status is acceptable after 12 months from treatment completion or after confirmed disease progression
13.	<u>9.5</u>	ATM expression was changed to ATM mutation status in exploratory endpoint analyses.
14.	Title Page	Corrected previously listed version date to November 13, 2024.

NCI Protocol #: 10405

Local Protocol #: 23-006

ClinicalTrials.gov Identifier: NCT04576091

TITLE: Phase I Trial of BAY 1895344 ATR Inhibitor Combined with Stereotactic Body Radiation Therapy and Pembrolizumab for Recurrent Head and Neck Squamous Cell Carcinoma

Corresponding Organization: LAO-PA015 / UPMC Hillman Cancer Center LAO

Principal Investigator/Translational PI: Yvonne Mowery, M.D., Ph.D.
UPMC Hillman Cancer Center
5150 Centre Avenue, 5th Floor
Pittsburgh, PA 15213
Phone: 412-623-4303
Fax: 412-647-1161
Email: yvm3@pitt.edu

Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / UPMC Hillman Cancer Center LAO
EDDO NC010 / Duke University-Duke Cancer Institute
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

Statistician:

Hong Wang, PhD
UPMC Cancer Pavilion
POB2, Suite 4C
5150 Centre Ave
Telephone: 412-383-1588
Email: how8@pitt.edu

NCI Protocol #: 10405
Version Date: September 9, 2024

Study Coordinator:

Julie Urban, PhD
UPMC Cancer Pavilion
5150 Centre Avenue
3rd Floor, Suite 301
Pittsburgh, PA 15232
Telephone: 412-623-7396
E-mail: urbanj2@upmc.edu
Study Team Email: ETCTN10405@upmc.edu

NCI-Supplied Agent: BAY 1895344 (NSC 810486)

Other Agent: Pembrolizumab (NSC 776864) (commercial)

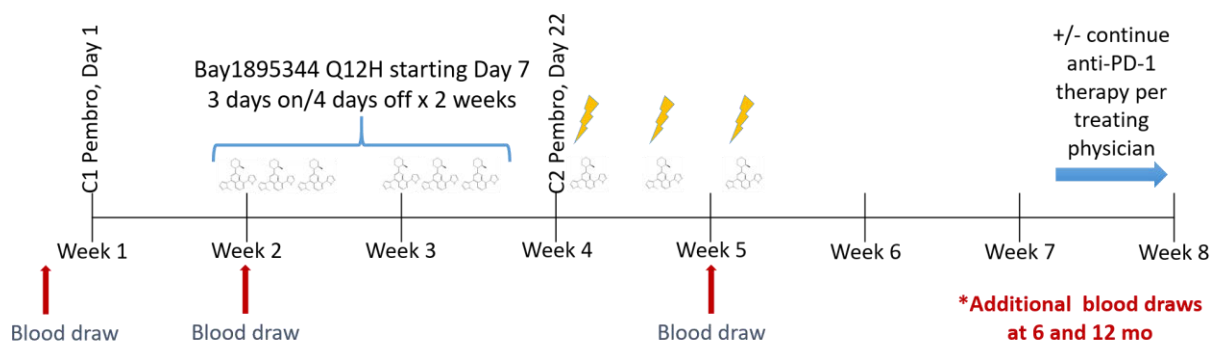
IND #: [REDACTED]

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / June 26, 2020
Revision 1 / August 19, 2020
Revision 2 / September 9, 2020
Revision 3a / November 2, 2020
Revision 4a / January 15, 2021
Revision 4 / February 2, 2021
Revision 5 / November 2, 2021
Revision 6 / November 15, 2021
Revision 7 / April 13, 2022
Revision 8 / November 25, 2022
Revision 9 / February 6, 2023
Revision 10 / March 28, 2023
Revision 11 / May 30, 2023
Revision 12 / November 13, 2023
Revision 13 / September 9, 2024

SCHEMA



Regimen Description

Agent	Dose	Route	Schedule	Cycle Length
BAY 1895344	Cycle 1: 30 mg Cycle 2: Dose as assigned	PO	Q12H Cycle 1: starting Day 7 (3 days on/4 days off) x 2 weeks Cycle 2: Q12H for 3 doses surrounding each SBRT fraction, administered within 1-6 hours before each fraction	21 days
Pembrolizumab	200 mg	IV	D1 of each cycle	21 days
SBRT	Dose as assigned (7 Gy x 3 or 8 Gy x 3)		Cycle 2: Starting between Days 2-8; 3 fractions with at least 2 days without radiation therapy and no more than 3 days without radiation therapy between fractions, e.g. Monday/Thursday/Monday	21 days

DOSE LEVELS

Dose Level	B1 (BAY)	B2 (BAY)	B3 (BAY)
A1 (SBRT)	7 Gy x 3 fractions 10 mg Q12H x 3 doses with each fraction	7 Gy x 3 fractions 20 mg Q12H x 3 doses with each fraction	7 Gy x 3 fractions 30 mg Q12H x 3 doses with each fraction
A2 (SBRT)	8 Gy x 3 fractions 10 mg Q12H x 3 doses with each fraction (STARTING	8 Gy x 3 fractions 20 mg Q12H x 3 doses with each fraction	8 Gy x 3 fractions 30 mg Q12H x 3 doses with each fraction

	DOSE)		
--	--------------	--	--

TABLE OF CONTENTS

SCHEMA	3
1. OBJECTIVES	8
1.1 Primary Objectives.....	8
1.2 Secondary Objectives.....	8
1.3 Exploratory Objective.....	8
2. BACKGROUND	8
2.1 Study Disease.....	8
2.2 CTEP Agent.....	9
2.3 Other Agent.....	14
2.4 Rationale	16
2.5 Correlative Studies Background	21
3. PATIENT SELECTION	25
3.1 Eligibility Criteria	25
3.2 Exclusion Criteria	28
3.3 Inclusion of Women and Minorities	30
4. REGISTRATION PROCEDURES	31
4.1 Investigator and Research Associate Registration with CTEP	31
4.2 Site Registration.....	32
4.3 Patient Registration.....	36
4.4 General Guidelines.....	37
5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES	38
5.1 Summary Table for Specimen Collection.....	38
5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies	39
5.3 Specimen Procurement Kits and Scheduling.....	39
5.4 Specimen Tracking System Instructions.....	40
5.5 Specimen Collection	44
5.6 Shipping Specimens from Clinical Site to the EET Biobank	45
5.7 Shipping of Specimens from Clinical Site to Other Laboratories	47
5.8 Biomarker Plan	49
5.9 Integrated Correlative Studies.....	51
5.10 Exploratory/Ancillary Correlative Studies	52
5.11 Special Studies	53
6. TREATMENT PLAN.....	54
6.1 Agent Administration.....	54
6.2 Definition of Dose-Limiting Toxicity.....	65
6.3 Dose Expansion Cohort	70
6.4 General Concomitant Medication and Supportive Care Guidelines.....	70
6.5 Duration of Therapy.....	72

6.6	Duration of Follow-Up	72
6.7	Criteria to Resume Treatment.....	72
6.8	Contraception and Pregnancy	73
6.9	Discontinuation of Treatment Following Complete Response.....	75
7.	DOSING DELAYS/DOSE MODIFICATIONS.....	75
7.1	BAY 1895344 Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events.....	75
7.2	Pembrolizumab Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events (revised 1-10-2023).....	76
8.	PHARMACEUTICAL INFORMATION.....	87
8.1	CTEP IND Agent.....	87
8.2	Commercial Agent.....	90
9.	STATISTICAL CONSIDERATIONS.....	91
9.1	Study Design/Endpoints.....	91
9.2	Sample Size/Accrual Rate.....	92
9.3	Stratification Factors	92
9.4	Analysis of Secondary Endpoints	92
9.5	Analysis of Exploratory Endpoints	93
10.	ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS	94
10.1	Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)	94
10.2	Adverse Event Characteristics	99
10.3	Expedited Adverse Event Reporting.....	100
10.4	Routine Adverse Event Reporting	103
10.5	Pregnancy.....	103
10.6	Secondary Malignancy.....	103
10.7	Second Malignancy.....	104
11.	STUDY CALENDAR	105
12.	MEASUREMENT OF EFFECT.....	108
12.1	Antitumor Effect – Solid Tumors	108
13.	STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS.....	114
13.1	Study Oversight	114
13.2	Data Reporting.....	115
13.3	Data Quality Portal	118
13.4	CTEP Multicenter Guidelines.....	118
13.5	Collaborative Agreements Language.....	119
14.	REFERENCES	121
APPENDIX A	PERFORMANCE STATUS CRITERIA	126

APPENDIX B	FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE.....	127
APPENDIX C	PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD	128
APPENDIX D	PATIENT MEDICATION DIARY	130
APPENDIX E	FUNCTIONAL ASSESSMENT OF CANCER THERAPY FOR PATIENTS WITH HEAD AND NECK CANCER (FACT-H&N), VERSION 4	134
APPENDIX F	PBMCS BLOOD SAMPLES REQUISITION FORM.....	138

1. OBJECTIVES

1.1 Primary Objectives

- 1.1.1 To evaluate the safety and tolerability of BAY 1895344 with concurrent head and neck stereotactic body radiation therapy (SBRT) reirradiation and pembrolizumab
- 1.1.2 To determine the recommended phase 2 dose (RP2D) of BAY 1895344 in combination with concurrent head and neck SBRT and pembrolizumab

1.2 Secondary Objectives

- 1.2.1 To observe and record anti-tumor activity (overall response rate, progression-free survival, and overall survival) of BAY 1895344, SBRT, and pembrolizumab for recurrent head and neck squamous cell carcinoma (HNSCC). Although the clinical benefit of this combination has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.3 Exploratory Objective

- 1.3.1 To identify predictive biomarkers of response to BAY 1895344, SBRT, and pembrolizumab, including, but not limited to the following: genetic alterations of ATM and other DNA damage response genes, tumor mutational load, circulating tumor DNA, baseline tumor ATM mutation status, tumor PD-L1 expression, and change in circulating Ki67+ CD8+ T-cells relative to baseline

2. BACKGROUND

2.1 Study Disease

Oral cavity, larynx and pharynx cancers account for approximately 3.7% of new cancer diagnoses in the United States, and head and neck cancer is the sixth leading type of malignancy worldwide (American Cancer Society, 2018; Union for International Cancer Control, 2014). Globally, more than 550,000 new cases are diagnosed each year, leading to approximately 380,000 deaths annually (Fitzmaurice *et al.*, 2017). Tobacco and alcohol use are major contributing factors to development of head and neck squamous cell carcinoma (HNSCC). Human Papillomavirus (HPV), primarily type 16, represents another etiologic factor for a rising number of HNSCC cases, particularly oropharyngeal cancers in North America and Western Europe (Chaturvedi *et al.*, 2011; O'Sullivan *et al.*, 2016). While clinical outcomes are generally favorable for HPV-related oropharyngeal cancer, prognosis remains poor for HPV-negative locally advanced HNSCC, with recurrence rates approaching 50% (Huang *et al.*, 2015). Surgery or radiotherapy (RT) alone is typically employed for early-stage head and neck cancer, while locally advanced disease generally requires cisplatin-based chemoradiation with or without surgical resection. Unfortunately, outcomes have been relatively stagnant for patients with

locally advanced HPV-negative HNSCC over the past 15 years, and locoregional recurrence is a major driver for mortality from HNSCC (Wen *et al.*, 2015; Chinn and Myers, 2015). Treatment options for recurrent disease after standard therapies remain limited, although immunotherapy with programmed cell death protein-1 (PD-1) inhibitors (pembrolizumab and nivolumab) have received Food and Drug Administration (FDA) approval for use in recurrent or metastatic head and neck cancer. Thus, there is an unmet need for new therapeutic approaches for patients with recurrent HNSCC.

Tumor recurrence within the radiation treatment field is the most common pattern of failure for HNSCC, suggesting persistence of radioresistant clones. Unfortunately, progressive growth of nodal and primary head and neck tumors often causes significant symptoms that are detrimental to patient quality of life, such as difficulty swallowing (*e.g.*, requiring feeding tube placement), pain, and airway obstruction necessitating tracheostomy tube placement. Therefore, reirradiation is often used to palliate symptoms or prevent complications from progressive disease that is likely to impact oral intake, breathing, and/or pain control. Reirradiation is among the treatment options recommended in National Comprehensive Cancer Network (NCCN) guidelines with or without systemic therapy in the setting of unresectable locoregional recurrent HNSCC. In a phase 2 prospective study of reirradiation plus cetuximab in patients with recurrent HNSCC, an SBRT regimen of 40-44 Gy delivered in 5 fractions on alternating days over 1-2 weeks was well tolerated (Vargo *et al.*, 2015). Grade 4 toxicities were not observed, and acute and late Grade 3 toxicities were each observed in 3 (6%) of 48 eligible patients.

2.2 CTEP Agent

2.2.1 BAY 1895344

DNA-damage response (DDR) is a multicomplex network of signaling pathways involved in detection and repair of DNA damage, transient cell cycle arrest to ensure genomic stability and cell viability (Fokas *et al.*, 2014; Zeman and Cimprich, 2014; Weber and Ryan, 2015). Deficiencies in DDR mechanisms have been shown to contribute to tumor development. Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) protein kinases are key regulators of DDR. They both contribute to maintaining genome integrity in response to various exogenous and endogenous genotoxic insults, *e.g.*, cytotoxic chemotherapy, ultraviolet light, ionizing radiation, or hypoxia (Fokas *et al.*, 2014; Pitts *et al.*, 2014; Yan *et al.*, 2014). Although ATR and ATM have broadly overlapping substrate specificities, they have non-redundant functions, which are well coordinated during DDR. ATR is a key replication-stress-response kinase (Cimprich and Cortez, 2008; Zeman and Cimprich, 2014; Fokas *et al.*, 2014; Wengner *et al.*, 2019). While ATM is primarily activated by DNA double-strand breaks (DSBs), ATR is recruited to regions of replication protein A (RPA)-coated ssDNA generated at stalled replication forks or during the of processing DSBs (Menezes *et al.*, 2015; Reaper *et al.*, 2011; Yan *et al.*, 2014). ATR phosphorylates/activates checkpoint kinase 1 (CHK1) at serine 345 (CHK1pS³⁴⁵), which stabilizes stalled replication forks until replication stress is resolved and DNA damage is repaired (Fokas *et al.*, 2014; Pitts *et al.*, 2014). Unlike normal cells, cancer cells are often deficient in ATM signaling, which renders them more reliant on the ATR-controlled S/G2-phase checkpoints for repairing DNA damage and survival (Fokas *et al.*, 2014; Menezes *et al.*, 2015; Reaper *et al.*, 2011). ATR inhibition in the ATM-signaling deficient tumors results in

synthetic lethality. Preclinical data suggest therapeutic utility of ATR inhibitors for cancer treatment as they may mediate synthetic lethality in DDR-deficient tumors and in combination with DNA-damaging agents (*e.g.*, radiation, cytotoxic chemotherapy), targeted therapies compromising DNA-damage repair, such as poly(ADP-ribose)polymerase (PARP) inhibitors or anti-androgen therapies may enhance their activity (Wengner *et al.*, 2019).

2.2.1.1 Nonclinical studies

Nonclinical *In Vitro* Activity and Mechanism of Action

BAY 1895344 is a highly potent and selective inhibitor of ATR kinase activity, with a 50% inhibitory concentration (IC₅₀) of 7 nmol/L of this enzyme (Investigator's Brochure, 2020; Luecking *et al.*, 2017). The activity and selectivity of BAY 1895344 were evaluated in biochemical assays against a panel of 395 kinases (Investigator's Brochure, 2020). Mechanistic target of rapamycin (mTOR) was identified as the most sensitive off-target kinase (IC₅₀=35 nmol/L). BAY 1895344 inhibited proliferation of a broad spectrum of human tumor cell lines with a median IC₅₀=78 nmol/L (mean IC₅₀=150 nmol/L). A clear separation between highly sensitive (IC₅₀ <100 nmol/L) and less sensitive cell lines was observed. The majority of sensitive cell lines were characterized by mutations affecting the ATM pathway. Lymphoma cell lines appeared to be most sensitive with IC₅₀s ranging from 8.6 to 32 nmol/L. BAY 1895344 effects against lymphoma cell lines were mostly cytotoxic, with induction of apoptosis observed in 61% of the tested cell lines (Gaudio *et al.*, 2019).

BAY 1895344 activity was evaluated in cellular mechanistic assays specific for inhibition of kinase activity of ATR, ATM, or DNA-dependent protein kinase (DNA-PK) catalytic subunits (DNA-PKcs) (Investigator's Brochure, 2020). The cellular level of phosphorylated H2AX (γH2AX) was used to monitor kinase activity of ATR, ATM and DNA-PKcs. By selection of appropriate cells and stimuli to induce either DSBs or replication stress, γH2AX served as a specific read-out for the activity of ATR, ATM or DNA-PKcs. In the ATR-specific mechanistic assay in HT-29 cells BAY 1895344 inhibited hydroxyurea-induced γH2AX with an IC₅₀ of 36 nmol/L. BAY 1895344 did not inhibit ATM- or DNA-PKcs-mediated H2AX phosphorylation up to a concentration of 10 μmol/L.

Nonclinical *In Vivo* Activity

In vivo, BAY 1895344 was evaluated in several human tumor xenograft models of different tumor indications (prostate cancer, mantle cell lymphoma [MCL], diffuse large B-cell lymphoma [DLBCL], cervical cancer, lung cancer, ovarian cancer, melanoma, colorectal cancer [CRC]) in mice (Investigator's Brochure, 2020). BAY 1895344 demonstrated strong antitumor activity with good tolerability as monotherapy at a dose of 50 mg/kg administered orally (PO) twice a day (BID) for 3 days followed by 4 days off treatment in biomarker-positive tumor models. BAY 1895344 had superior antitumor effects compared to other ATR inhibitors (AZD-6738, VX-970, or VX-803) as well as a PARP inhibitor, olaparib, in several tumor models. BAY 1895344 showed synergistic antitumor effects in combination with DNA damage inducing therapy, such as chemotherapy (cisplatin, carboplatin, oxaliplatin, 5-FU, irinotecan) (Investigator's Brochure, 2020), α-radiation by radium-223 dichloride (Wengner *et al.*, 2018; Bannik *et al.*, 2019) or thorium 227 (Wickstroem *et al.*, 2019a; Wickstroem *et al.*, 2019b), external beam radiation therapy [EBRT] (Wengner *et al.*, 2020), therapies compromising DNA

damage repair such as a PARP inhibitor olaparib (Wengner *et al.*, 2020) or anti-androgen agent darolutamide (Wengner *et al.*, 2020), therapies targeting a programmed cell death protein 1 (PD1), PD ligand 1 (PD-L1), or other targeted therapies (PI3K inhibitor) (Investigator's Brochure, 2020).

Nonclinical Pharmacology

Following single intravenous (IV) administration of BAY 1895344, a high volume of distribution (V_d) was observed in all species (mice, rats, and dogs) (Investigator's Brochure, 2020). In mice and dogs, elimination of the drug was bi-phasic with a short initial (distribution phase) half-life ($t_{1/2}$) of 0.2 and 1 hour, respectively, followed by a long elimination $t_{1/2}$ of 12.2 and 8.3 hours, respectively. In rats only the distribution phase $t_{1/2}$ (1.3 hours) was observed.

Following single oral dosing of BAY 1895344, the elimination $t_{1/2}$ was intermediate to long in rats and could not be calculated in dogs (Investigator's Brochure, 2020). In single dosing studies in dogs, plasma exposure measured as an area under the concentration time curve (AUC) increased more than dose-proportionally over the dose range of 3-8 mg/kg, whereas a maximum concentration (C_{max}) increased dose-proportionally. After multiple oral dosing of BAY 1895344, AUC and C_{max} on day 17 were lower than on day 1 in rats. In dogs, exposure increased only slightly between days 1 and 23. Oral bioavailability was moderate to high (67%- 87%) in rats and moderate in dogs (51%). The binding of BAY 1895344 to plasma proteins was low to moderate in all investigated species. A slight concentration dependency was observed with a decrease in protein binding at the highest test concentrations (increase in the unbound fraction from 2.6% to 4.2% in humans).

Hepatic route appears to be the key clearance mechanism for this compound (Investigator's Brochure, 2020). Metabolic pathways were highly comparable across all investigated species. In human hepatocytes, BAY 1895344 was metabolized *via* oxidation and dealkylation at the methylmorpholine moiety and direct glucuronidation. Oxidative metabolism was mainly catalyzed by cytochrome P450 (CYP) isoform 3A4 (CYP3A4). BAY 1895344 appears to have a potential to inhibit as well as induce CYP3A4. BAY 1895344 showed the inhibitory potential towards protein transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), with IC_{50} of 7.4 μ M and 1.9 μ M, respectively. BAY 1895344 had the inhibitory potential toward organic anion transporting polypeptide (OATP)1B1 and OAT1B3.

Nonclinical Safety and Toxicology

Safety pharmacology studies revealed no effect on the human ether-a-go-go-related (hERG) potassium tail current was observed (Investigator's Brochure, 2020). No clinically relevant or major effects were observed on the central nervous system (CNS). Cardiovascular examinations revealed a moderate increase in diastolic blood pressure without clear effects on systolic blood pressure. ECG intervals were not substantially influenced.

Major target organs for BAY 1895344 in oral repeat-dose toxicity studies in rats and dogs with continuous and intermittent (3 days on/4 days off) dosing were the lymphatic organs and bone marrow, epithelial tissues including skin and gastrointestinal (GI) tract, and male reproductive organs (Investigator's Brochure, 2020). Additional toxicity observed in adult animals was atrophy of bone spongiosa in both species. All findings were reversible.

BAY 1895344 showed genotoxicity *in vitro* (micronucleus test in Chinese hamster cells for aneugenicity and clastogenicity) and *in vivo* (bone marrow [BM] micronucleus test in rats after a 4-week repeat dosing) (Investigator's Brochure, 2020).

No specific studies on reproductive and developmental toxicity of BAY 1895344 were conducted at this stage of development. (Investigator's Brochure, 2020). Degenerative findings in male reproductive organs were seen in 4-week repeat-dose toxicity studies in rats and dogs. Thus, an influence on fertility can be expected. Homozygous ATR knock-out mice are embryo-lethal, indicating that ATR is essential in embryogenesis. Based on its mode of action, BAY 1895344 is regarded as a potential teratogen.

There was an indication for phototoxicity in an *in vitro* assay (Investigator's Brochure, 2020).

Overall, BAY 1895344 displayed an acceptable nonclinical safety profile to initiate clinical development in patients with advanced disease (Investigator's Brochure, 2020). The toxicities observed are regarded as monitorable and/or manageable in humans.

2.2.1.2 Clinical studies

Preliminary clinical experience is derived from the ongoing company-sponsored First-in-Human (FiH) study of BAY 1895344 (data cut-off date June 16, 2020) (Investigator's Brochure, 2020).

Clinical Pharmacokinetics

Preliminary pharmacokinetics (PK) show that BAY 1895344 administered at the maximum tolerated dose (MTD) of 40 mg PO BID for 3 days every week (3 days on/4 days off) in patients with advanced solid tumors was absorbed rapidly with a median time to reach maximum drug concentration (t_{max}) of 1 hour and a geometric mean terminal $t_{1/2}$ of 9.69 hours in plasma (Investigator's Brochure, 2020). Exposure increase was observed to be broadly dose-proportional across the dose range investigated (5-80 mg), and accumulation was consistent with observed $t_{1/2}$. Clinical exposure was observed to be in the range associated with efficacy in nonclinical models.

Clinical Safety

A. Dose-escalation cohort

Dose-limiting toxicities were observed with BAY 1895344 administered at doses 60 mg BID and 80 mg BID, as well as on the intermittent schedule of 60 mg BID 3 days on/4 days weekly for 2 weeks of a 3-week cycle (Investigator's Brochure, 2020). BAY 1895344 administered at 40 mg PO BID on the 3-day-on/4-day-off schedule every week on a 3-week cycle has been declared the MTD.

All 50 patients who started BAY 1895344 treatment in the dose-escalation phase (as of June 16, 2020) experienced at least one treatment-emergent adverse event (TEAE), and 94.0% of patients experienced at least one BAY 1895344-related TEAE of any grade; 61.5% had grade 3, and 17.9% had grade 4 (Investigator's Brochure, 2020). The most common study drug-related TEAEs by (occurring in $\geq 10\%$ of patients) were: anemia (76.0%), neutropenia (44.0%), fatigue

(38.0%), nausea (34.0%), white blood cell (WBC) count decreased (24.0%), neutrophil count decreased (22.0%), platelet count decreased, thrombocytopenia, and decreased appetite (18.0% each), diarrhea (12.0%, and vomiting (10.0%). Overall, 36.0% of patients experienced at least one treatment-emergent serious adverse event (TESAE) in the dose-escalation phase and 8.0% of patients experienced at least one BAY 1895344-related TESAE: medication error, grade 4 neutropenia, grade 3 anemia, diarrhea, nausea, and hypotension (2.0% each). One patient each on the 40 mg BID and 80 mg BID cohorts died within 30 days of treatment discontinuation, but the deaths were assessed as unrelated to the study drug.

B. Expansion cohort

At least one TEAE was observed in 97.7% of patients (127/130) treated at the MTD and at least one BAY 1895344-related TEAE of any grade was experienced by 93.8% of patients, grade 3 (in 69.2% of patients), grade 4 (in 16.2% of patients), and grade 5 (in 3.8% of patients) (Investigator's Brochure, 2020). The most common drug-related TEAEs (occurring in $\geq 10\%$ patients) were: anemia (81.5%), neutropenia (43.8%); fatigue (31.5%), nausea (28.5%), WBC count decreased (20.8%), neutrophil count decreased and thrombocytopenia (17.7% each), vomiting (14.6%), and platelet count decreased (10.8%). Eight patients (6.2%) experienced at least one BAY 1895344-related TESAE. There were seven deaths in the expansion cohort occurring within 30 days of permanent treatment discontinuation, and all were considered unrelated to the study drug.

Guidance for Investigators Summary (Investigator's Brochure, 2020)

Based on BAY 1895344 preclinical findings and its mode of action, BAY 1895344 has a genotoxic potential (Investigator's Brochure, 2020). The compound was phototoxic in an *in vitro* assay, so that patients should avoid direct exposure to sunlight as a precaution. Effects on male reproductive organs were found, so that male fertility may be impaired. In addition, embryo-fetal toxicity including teratogenicity are expected for BAY 1895344 based on its mode of action. Therefore, women of child-bearing potential should use effective contraceptive measures during treatment, and pregnant women should be excluded from studies of BAY 1895344. Men should use barrier contraception when having sexual intercourse with women of child-bearing potential. In addition, breast-feeding should be discontinued during treatment.

Drug-Drug Interactions

BAY 1895344 bears a potential risk to have a weak to moderate inhibitory potential on sensitive CYP3A4 substrates (*e.g.*, midazolam), possibly resulting in clinically relevant drug-drug interactions. BAY 1895344 was also shown to be an inducer of CYP3A4 *in vitro* (Investigator's Brochure, 2020). However, this induction potential may be alleviated by administering BAY 1895344 on the intermittent dosing schedule (3 days on/4 days off). Medications that are a) predominantly metabolized by CYP3A4 and have a narrow therapeutic window and b) strong CYP3A4 inducers and inhibitors have been prohibited in the BAY 1895344 FiH study.

- Prohibited strong inhibitors of CYP3A4: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and

(ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, and voriconazole

- Prohibited strong inducers of CYP3A4: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort
- Prohibited drugs that are CYP3A4 substrates and have narrow therapeutic index: alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus.

Undesirable effects with a causal relationship to BAY 1895344 in Humans (Investigator's Brochure, 2020)

- Anemia: 89% (any grade); 66% (grade ≥ 3)
- Neutropenia: 60% (any grade); 48% (grade ≥ 3)
- Thrombocytopenia (28%); 10% (grade ≥ 3)

The hematological disorders caused by BAY 1895344 are in line with the mode of action of the compound targeting rapidly dividing cells in the hematopoietic system and leading to bone marrow suppression.

BAY 1895344 Dose and Schedule in Humans

In the FiH study, BAY 1895344 40 mg PO BID administered with the 3 days on/4 days off weekly schedule on a 21-day cycle was declared the MTD (Investigator's Brochure, 2020).

2.3 Other Agent

2.3.1 Pembrolizumab

Pembrolizumab has high affinity and potent receptor-blocking activity for the PD-1 receptor, based on preclinical *in vitro* data (Investigator's Brochure, 2020). Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis *et al.*, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8⁺ T-cells and the ratio of CD8⁺ effector T-cells/FoxP3⁺ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma (Dudley *et al.*, 2005; Hunder *et al.*, 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under

healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 [PD-L1] and/or programmed cell death ligand 2 [PD-L2]) (Greenwald *et al.*, 2005; Okazaki *et al.*, 2001).

The structure of murine PD-1 has been resolved (Zhang *et al.*, 2004). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP 1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Chemnitz *et al.*, 2004; Sheppard *et al.*, 2004; and Riley, 2009). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry *et al.*, 2005; Francisco, 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in head and neck cancer.

2.3.1.1 Pembrolizumab Background and Clinical Trials

Pembrolizumab (Keytruda®), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co. for the treatment of cancer. Pembrolizumab is approved for treatment of melanoma in several countries; in the United States (US) and European Union it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by a FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. Pembrolizumab is approved in the US for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Pembrolizumab has demonstrated initial clinical efficacy in single-arm monotherapy trials in patients with NSCLC, HNSCC, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure (2020).

2.4 Rationale

2.4.1 Rationale for Pembrolizumab Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg administered every 3 weeks (Q3W). The dose approved in the US and several other countries for treatment of melanoma patients is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

The initial phase 1 study of pembrolizumab (KN001) evaluated 5 dose levels (1 mg/kg every 2 weeks [Q2W], 3 mg/kg Q2W, 10 mg/kg Q2W, 2 mg/kg Q3W, and 10 mg/kg Q3W) in patients with advanced solid tumors. All 5 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No MTD has been identified to date. In addition, 2 randomized cohort evaluations of melanoma patients receiving MK-3475 2 mg/kg or 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W or 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of any important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. The PK properties of pembrolizumab, specifically the weight-dependency in clearance and volume of distribution, are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in patients with melanoma can be expected. As the antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, it is rendered independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses across tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

2.4.2 Rationale for the Study

Several studies have demonstrated that ATR/CHK1 pathway inhibition can radiosensitize cancer cells (Sankunny *et al.*, 2014; Fokas *et al.*, 2014; Dillon *et al.*, 2017; Tu *et al.*, 2018; Fujisawa *et al.*, 2015). BAY 1895344 is a potent and selective small molecule ATR inhibitor that has been shown to be well-tolerated in a recent phase I trial in patients with advanced solid tumors. Responses to BAY 1895344 were observed in patients with *ATM* mutation or loss of *ATM* protein expression (De Bono *et al.*, 2019). An unpublished preclinical study in a human colorectal cancer xenograft mouse model (LoVo) demonstrated significantly improved tumor growth delay with the addition of BAY 1895344 (50 mg/kg PO, 2 days on/5 days off) to radiation therapy (RT; 5 Gy administered at day 12 and day 27 post-tumor inoculation) (**Figure 1**). Interestingly, ATR inhibition has also been shown to increase antigen presentation, immune cell infiltrate, and anti-tumor T cell activity when combined with RT (Vendetti *et al.*, 2018; Dillon *et al.*, 2019). The combination of ATR inhibitor AZD6738 and RT caused significant tumor growth delay in a syngeneic transplant mouse model of colorectal cancer (CT26) and autochthonous model of lung adenocarcinoma (*Kras*^{G12D}/*Twist1*). Furthermore, a subset of mice in the CT26 model exhibited a complete response to AZD6738 and RT. Complete responders were resistant to tumor rechallenge, indicative of immunologic memory. While RT is associated with increased tumor cell surface expression of the immunoinhibitory protein programmed cell death ligand 1 (PD-L1), ATR inhibition abrogated this effect. Furthermore, combination of RT and ATR inhibition with AZD6738 led to increased CD8⁺/Treg ratio. These findings indicate an interplay between ATR inhibition and the immune system. Indeed, another preclinical study in the CT26 mouse model demonstrated synergy between ATR inhibition with BAY 1895344 and immune checkpoint blockade with anti-PD-1 antibody (Wengner *et al.*, 2019). Interestingly, this cooperative effect was sequence-dependent and observed only when anti-PD-1 therapy preceded BAY 1895344 (**Figure 2**).

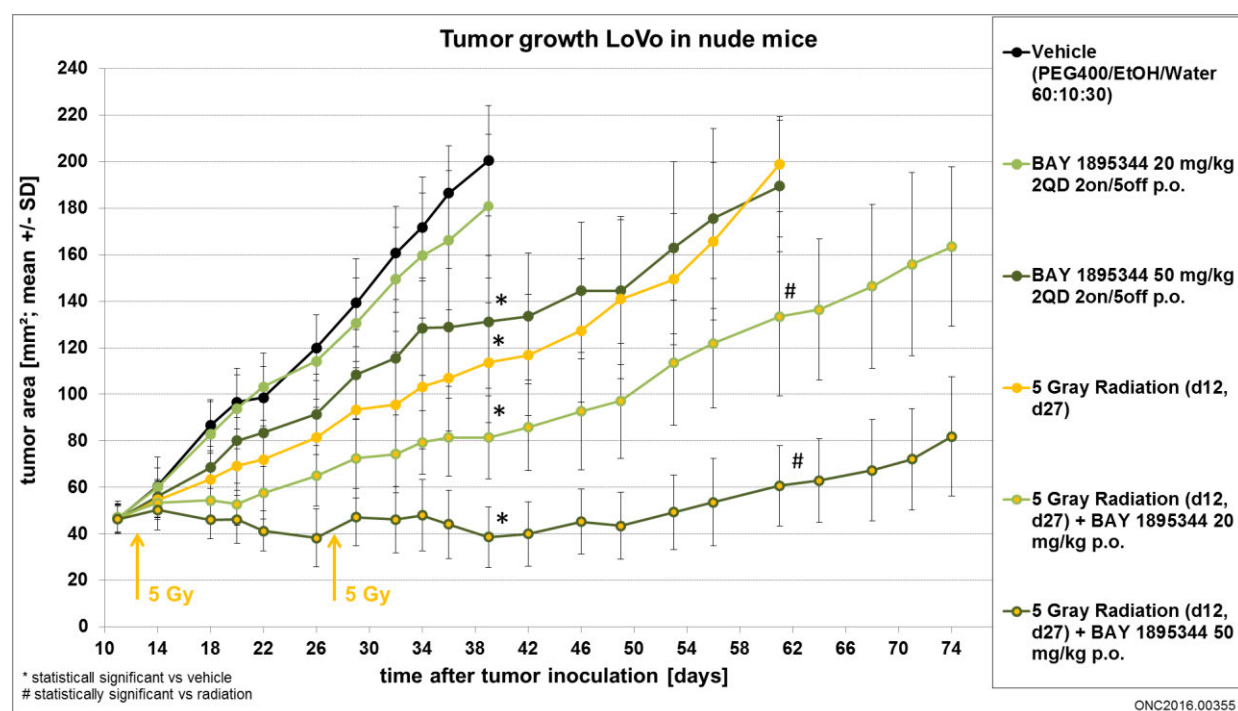


Figure 1: Xenografts were established in nude mice with the LoVo human colorectal cancer cell line. When tumors reached approximately 50 mm³, treatment was initiated with vehicle, Bay 1895344 (20 mg/kg or 50 mg/kg, 2 days on and 5 days off), two fractions of radiotherapy (5 Gy on days 12 and 27), or the combination of BAY 1895344 and radiotherapy. Tumors were measured by calipers thrice weekly. Treatment with BAY 1895344 at 50 mg/kg or radiotherapy caused significant growth delay relative to vehicle. Treatment with the combination of BAY 1895344 and radiotherapy caused a significant growth delay relative to radiotherapy alone, with a greater effect observed with the higher BAY 1895344 dose (50 mg/kg).

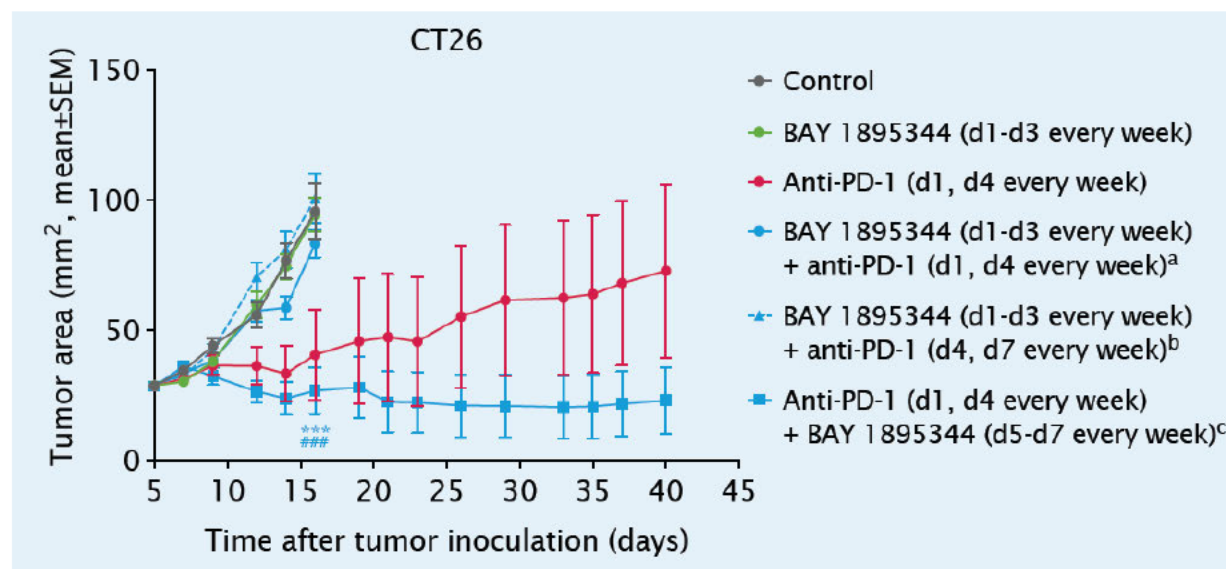


Figure 2: Tumors were established in syngeneic mice with the CT26 murine colorectal cancer cell line. When tumors reached approximately 20 mm³, treatment was initiated with vehicle, BAY 1895344, anti-PD-1 antibody, or the combination of BAY 1895344 and anti-PD1 antibody. Tumors were measured by calipers thrice weekly. Treatment with anti-PD-1 therapy (days 1 and 4, weekly) prior to BAY 1895344 (days 5-7, weekly) led to a significant tumor growth delay relative to control, BAY 1895344 alone, or anti-PD-1 therapy alone. No tumor growth delay was observed if BAY 1895344 treatment preceded anti-PD-1 treatment.

In vitro assays also demonstrate that single-agent BAY 1895344 has cytotoxic activity in murine and human HNSCC cell lines (**Figure 3**). While the half maximal inhibitory concentration (IC₅₀) for the HNSCC cell lines is <0.3 mcM, the IC₅₀ for the normal tissue control (IMOK) is >2.5 mcM. This indicates selective cytotoxicity for HNSCC relative to oral keratinocytes.

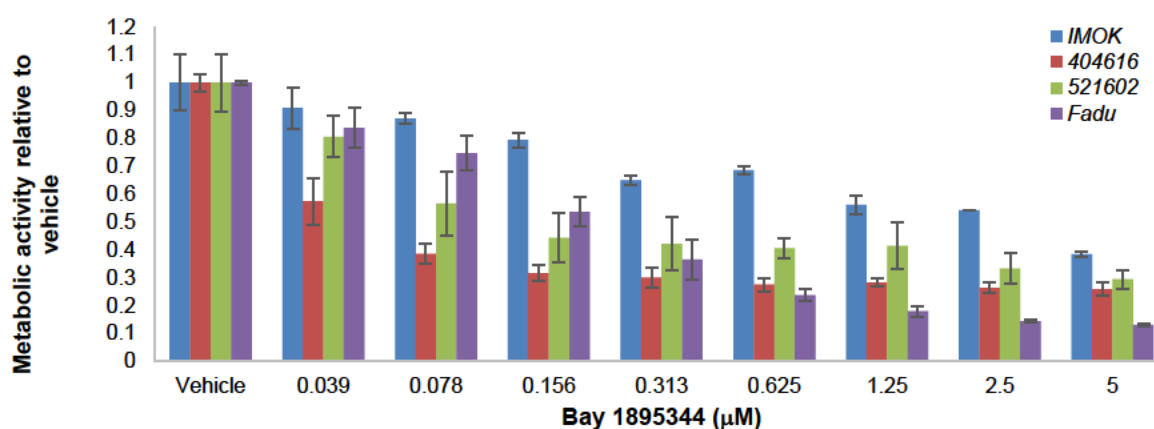


Figure 3: MTT Assay was performed on cell lines (IMOK = immortalized murine oral keratinocytes; 404616 and 521602 = murine primary oral cavity SCC cell lines; Fadu = human hypopharynx SCC cell line) treated for 72 hours with vehicle or serial dilutions of BAY 1895344 in triplicate. Absorbance at 660 nm (reference) was subtracted from absorbance at 580 nm, and values were normalized relative to treatment with vehicle. Mean and standard deviations are shown for each treatment.

BAY 1895344 is currently being tested in patients with advanced solid tumors in a phase I clinical trial (NCT03188965) (De Bono *et al.*, 2019). At the 2019 American Society of Clinical Oncology Annual Meeting, initial results for the single-agent dose escalation cohort were reported. Eighteen patients with metastatic solid malignancies were treated across six cohorts (5 mg, 10 mg, 20 mg, 40 mg, 60 mg, or 80 mg twice daily). While no DLTs were reported for patients treated with 5-40 mg, there were 2/7 DLTs in the 60 mg cohort and 2/3 DLTs in the 80 mg cohort. Therefore, 40 mg twice daily, 3 days on/4 days off, was defined as the MTD. The most common adverse events were anemia, neutropenia, nausea, and fatigue. Paired tumor biopsies pre- and post-treatment demonstrated modulation of phospho- γ H2AX and/or phospho-Kap1 by BAY 1895344 treatment. An objective response rate of 30.7% was reported for 13 patients receiving ≥ 40 mg twice daily. Notably, all responders of this single-agent therapy exhibited *ATM* mutation or loss of ATM protein expression. A dose expansion cohort for this trial is ongoing. Given the limited single-agent activity of BAY 1895344 in patients without DDR deficiency, combination with DNA-damaging agents such as radiation therapy warrants further investigation. Notably, a second phase I clinical trial recently opened to determine the RP2D of BAY 1895344 in combination with pembrolizumab (NCT04095273). Eligibility criteria for this study included confirmed diagnosis with a DDR deficiency biomarker-positive malignancy.

No ongoing clinical trials are evaluating BAY 1895344 in combination with radiation therapy, nor are any BAY 1895344 trials specifically enrolling patients with HNSCC. Given the limited treatment options and median survival <15 months for patients with recurrent, unresectable HNSCC, the current clinical trial will focus on this patient population. Furthermore, HNSCC commonly demonstrates ATM deficiency due to distal 11q loss (Sankunny *et al.*, 2014), and ATM loss has been associated with response to BAY 1895344. Pembrolizumab is FDA-approved for patients with recurrent HNSCC, and preclinical data presented above indicate promising interactions between BAY 1895344 and PD-1 inhibition. Finally, *in vitro* (data not shown) and *in vivo* (**Figure 1**) preclinical studies demonstrate that BAY 1895344 radiosensitizes tumor cells. Thus, the proposed trial evaluating BAY 1895344 with concurrent pembrolizumab and SBRT reirradiation has strong rationale and addresses an unmet clinical need. Potential safety concerns with this combination include increased risk of acute and late RT-related toxicities, including mucositis, xerostomia, fatigue, dysphagia/feeding tube requirement to meet nutritional needs, osteoradionecrosis of the mandible, fistula formation, and carotid blowout. However, a previous phase 2 study (NCT01104922) of reirradiation (40-44 Gy in 5 fractions on alternating days over 1-2 weeks) plus cetuximab in patients with recurrent HNSCC suggests the proposed RT combination regimen will be well tolerated (Vargo *et al.*, 2015). There were no grade 4 or 5 toxicities, and the rates of both acute and late CTCAE grade 3 toxicities were 6%. NCCN Guidelines Version 2.2020 discuss head and neck reirradiation with SBRT for patients with careful selection, cautioning its use in patients with circumferential carotid artery involvement and indicating that the best results are observed in patients with smaller tumor volume and no skin involvement. Typical SBRT schedules for reirradiation range from 35 to 44 Gy in 5 fractions (7-8.8 Gy/fraction). Due to the radiosensitizing effect of BAY 1895344 observed in preclinical *in vitro* and *in vivo* studies, the radiation dose regimen has been reduced in the current study (7-8 Gy $\times$ 3 fractions). If this study demonstrates that this therapeutic combination is safe with promising efficacy signal, then this would likely lead to a phase 2 clinical trial in which patients would be randomized to receive pembrolizumab and BAY

1895344 with or without concurrent radiotherapy.

2.5 Correlative Studies Background

2.5.1 ATM Mutation Status

Up to 50% of HNSCCs exhibit distal 11q loss, which has been associated with poor prognosis and reduced radiosensitivity (**Figure 4**) (Sankunny *et al.*, 2014). Notably, the distal 11q locus contains several DNA damage response genes including *ATM*. DNA double-strand breaks trigger activation of the ATM kinase, leading to phosphorylation of checkpoint kinase 2 (CHK2) and activation of downstream signaling to cause cell cycle arrest, DNA repair, and/or apoptosis (**Figure 5**). Thus, ATM plays an active role in cellular responses to DNA-damaging agents, such as radiation therapy and cisplatin. *ATM* copy number loss may increase dependence on the ATR pathway for response to DNA damage. A recent study utilizing human oral squamous cell carcinoma cell lines demonstrated that *in vitro* inhibition of ATR/CHK1 signaling enhanced radiosensitivity in cells with distal 11q loss (**Figure 6**), which suggests that targeting ATR may improve radiation response in HNSCC (Sankunny *et al.*, 2014). Thus, we hypothesize that patients with mutant *ATM* will exhibit improved response to ATR inhibition with BAY 1895344 compared to patients with intact *ATM*.

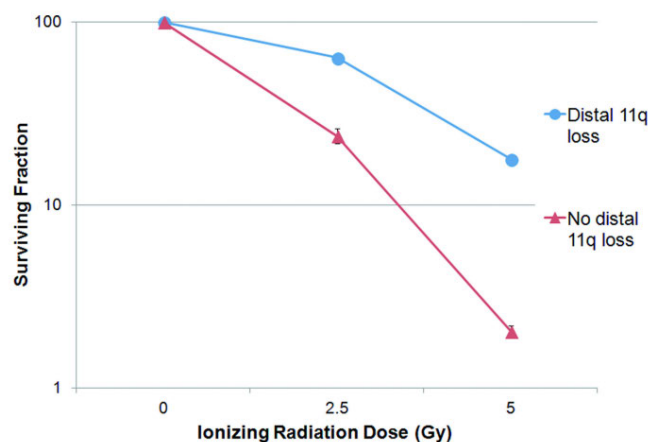


Figure 4: Clonogenic assay demonstrating relative radioresistance of oral cavity squamous cell carcinoma cell lines with distal 11q loss relative to cell lines without distal 11q loss.

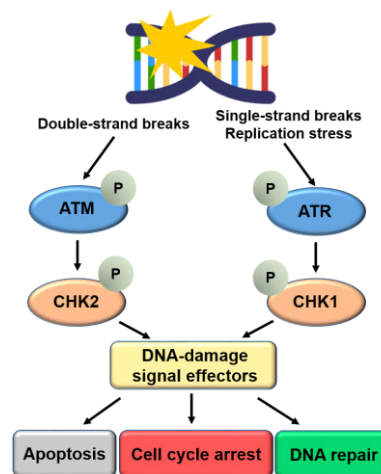


Figure 5: Schematic of ATM and ATR-mediated DNA damage response pathways.

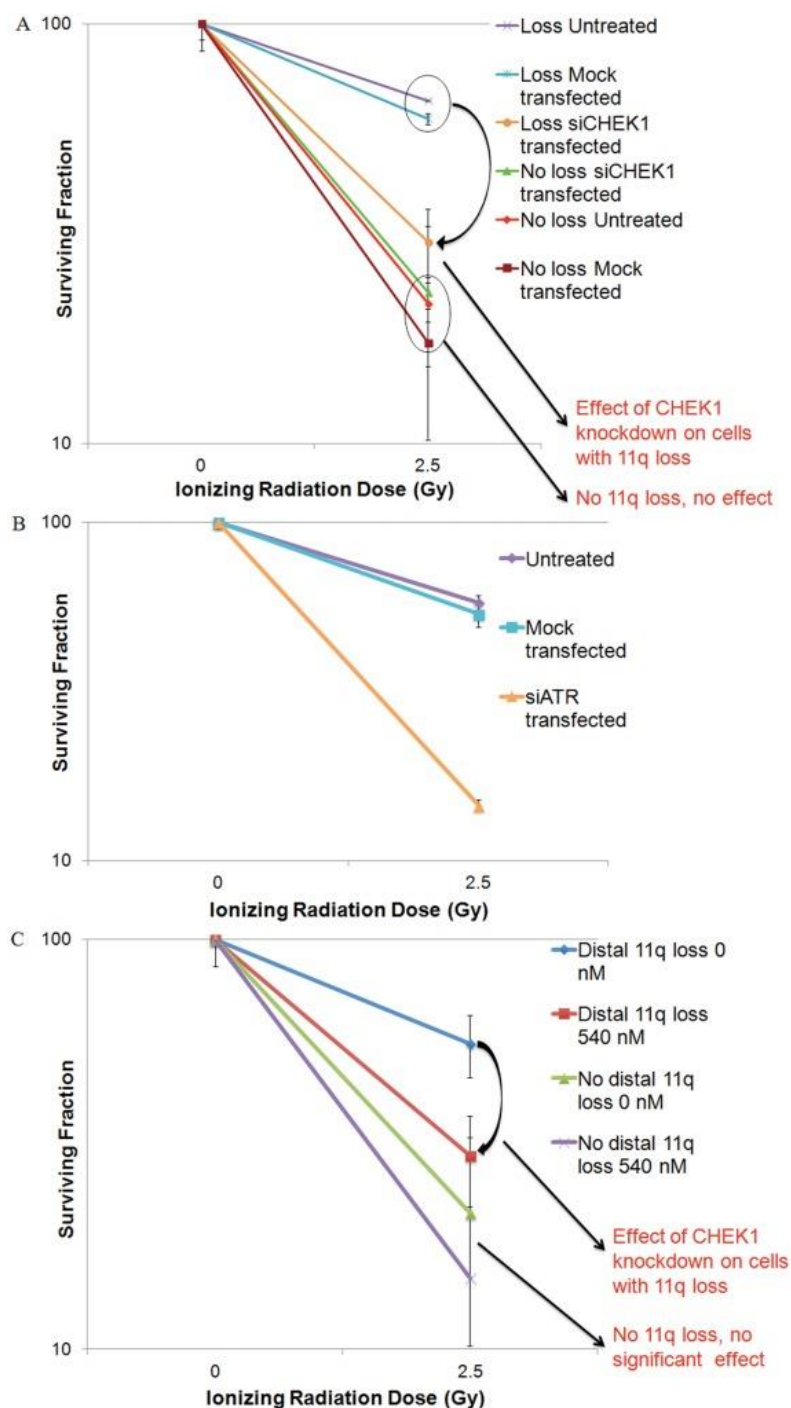


Figure 6: Clonogenic assays demonstrate survival of oral cavity squamous cell carcinoma cell lines after 0 Gy or 2.5 Gy radiation therapy and knockdown of CHEK1 or ATR using siRNA or a small molecule inhibitor (SMI) of CHEK1 (PF-00477736). Surviving fraction is plotted on a logarithmic scale with error bars (6SEM). (A) Transfection of cells harboring “distal 11q loss” with siRNA targeting CHEK1 leads to decreased survival compared to untreated or mock-transfected cells. Transfection with siRNA targeting CHEK1 does not affect survival of cells with “no distal 11q loss” after RT. (B) Transfection of cells harboring “distal 11q loss” with siRNA targeting ATR leads to decreased survival compared to untreated or mock-transfected cells. (C) RT combined with SMI of CHEK1 resulted in increased killing of cells with distal 11q loss relative to RT alone, but no significant difference in survival for cells without distal 11q loss.

2.5.2 PD-L1 Expression

This trial includes treatment with pembrolizumab, a monoclonal antibody targeting the PD-1/PD-L1 axis. Positive PD-L1 expression has been associated with improved overall response rate (ORR) and overall survival (OS) for patients with recurrent and metastatic HNSCC who receive pembrolizumab and other drugs targeting PD-1/PD-L1 (see table below from Oliva *et al.*, 2019).

We hypothesize that patients with PD-L1⁺ tumors will have better ORR and OS than patients with PD-L1⁻ tumors.

Anti-PD-1/PD-L1 agents tested in recurrent and metastatic HNSCC

Agents	Target	Phase/study	N	PD-L1 expression Location	Cut-off	ORR (%)			OS (HR) ^a		
						Overall	PD-L1 ⁺	PD-L1 ⁻	Overall	PD-L1 ⁺	PD-L1 ⁻
Nivolumab	PD-1	III (CHECKMATE-141)	240	TCs	>1%	13.3%	17%	11.8%	0.68	0.55	0.73
Pembrolizumab	PD-1	I (KEYNOTE-012)	132	TCs+ICs	>1%	18%	22 %	4%	NA	NA	NA
				TCs only	>1%		17 %	7%			
		III (KEYNOTE-040)	247	TCs+ICs(CPS)	CPS > 1%	14.6%	17.3%	Ø	0.80 (P 0.016)	0.74 (P 0.0049)	Ø
				TCs (TPS)	TPS > 50%		26.6%	Ø		0.53 (P 0.0014)	Ø
		III (KEYNOTE-048)	882	TCs+ ICs (CPS)	CPS>1	Ø	19.1%	Ø	Ø	0.78 (P 0.0086)	Ø
					CPS>20		23.3%	Ø		0.61 (P 0.0007)	Ø
Durvalumab	PD-L1	I (MEDI4736-1108)	62	TCs	>25%	10%	18%	8%	NA		NA
		II (HAWK)	112	TCs	>25%	NA	16.2%	NA	NA		
		II (CONDOR)	67	TCs	<25%	NA	NA	6%	0.99 (P 0.89)		
Atezolizumab	PD-L1	I (GO27831)	32	ICs	IC2/3: >5% IC0/1: <5%	22%	24%	14%	NA		NA

^aHR for OS resulting from: nivolumab and pembrolizumab versus investigator's choice of chemotherapy (Docetaxel, Methotrexate and Cetuximab) in the CHECKMATE-141 and KEYNOTE-040 studies, respectively; pembrolizumab monotherapy versus EXTREME regimen in the KEYNOTE-048 study; durvalumab versus tremelimumab plus durvalumab in the CONDOR study.

ORR, overall response rate; OS, overall survival; HR, hazard ratio; TCs, tumor cells; ICs, immune cells; CPS, number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100; TPS, percentage of tumor cells with membranous PD-L1 expression; NA, not applicable; Ø, no data available.

Oliva *et al.* 2019

2.5.3 Peripheral Blood Mononuclear Cells

Two recent studies (Kamphorst *et al.*, 2017; Huang *et al.*, 2019) have demonstrated that the change in Ki-67⁺ CD8⁺ T cells relative to baseline is predictive of response to PD-1 therapy for NSCLC and melanoma, respectively. Kamphorst *et al.* demonstrated minimal changes in Ki-67⁺ CD8⁺ T cells in healthy volunteers over a 2-week period, in contrast to significant increases observed in NSCLC patients after receiving anti-PD-1 therapy (nivolumab). Patients with early proliferative T cell responses after anti-PD-1 therapy were more likely to demonstrate clinical responses. Huang *et al.* also demonstrated that T cell responses in the peripheral blood correlated with tumor infiltrating lymphocyte response.

We will test the hypothesis that concurrent BAY 1895344 with pembrolizumab and subsequently with SBRT at the MTD will increase Ki67⁺ CD8⁺ T cells compared to baseline, which will correlate with treatment response (ORR and progression-free survival [PFS]). The primary exploratory endpoint will be the log₂ (fold-change) in the percentage of Ki67⁺ CD8⁺ T cells between baseline and Week 5. Differences between baseline and Week 2, 6 months and 12 months will also be investigated. Subpopulations that are PD-1+ and/or CTLA-4+ will also be evaluated.

With data available on 16 (of 18) patients treated at the MTD, power is approximately 80% to detect a mean log₂ (fold-change) of 0.6 at Week 5 assuming a standard deviation of 0.9 (1-

sample t-test; 1-sided $\alpha=0.05$). Differences in $\log_2$ (fold-change) between responders and non-responders will be compared descriptively.

Below is the distribution from Kamphorst *et al.* (**Figure 7**), and we expect a similar distribution in the current study's patient population with slightly fewer patients reaching the 1.5-fold cutpoint.

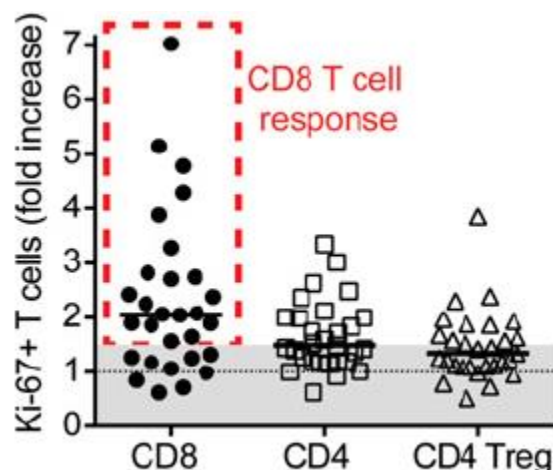


Figure 7: Peripheral blood samples were collected from patients with NSCLC at baseline and every 2-3 weeks prior to nivolumab infusion for up to six cycles. Flow cytometry was performed to detect the frequency of Ki-67+ cells among CD8+ T cells, CD4+ T cells, and Foxp3+ CD4+ regulatory T cells (Treg). The best fold increase in Ki-67+ cells among each T cell population is shown. The gray shaded area denotes a 1.5 fold threshold. The lines represent median fold change.

Kamphorst *et al.*, 2017

2.5.4 Whole Exome Sequencing (WES)

WES will be performed on archival tumor samples, with normal PBMCs as a matched germline control for each patient. WES will provide baseline tumor mutational load, mutation status of DNA damage response genes, and genetic profiling necessary to evaluate circulating tumor DNA. Several studies have demonstrated that greater tumor mutational load correlates with improved efficacy of immunotherapy, although elevated mutational burden is not sufficient for treatment response (Snyder *et al.*, 2014; Le *et al.*, 2015; Rizvi *et al.*, 2015; Kim *et al.*, 2019). We will test the hypothesis that patients with tumors with high tumor mutation burden (above median for patients enrolled on study) at baseline will have better response rate and survival relative to patients with low tumor mutation burden (equal to or below median). In addition, BAY 1895344 has demonstrated increased efficacy with tumors harboring deficiencies in DNA damage response genes, such as *ATM*, *MSH3*, *RAD50*, *FANCD2*, *ARID1A* and *PRKDC* (Wengner *et al.*, 2020). Thus, overall response rate and progression-free survival will be correlated with baseline gene mutation signatures with a particular focus on DNA damage response gene deficiencies.

2.5.5 Circulating tumor DNA (ctDNA) Sequencing

Circulating tumor DNA will be quantified in peripheral blood samples obtained prior to initiating therapy (mandatory) and at the time of disease progression (optional). Analysis of DNA damage response-related genes in circulating tumor DNA will be correlated with overall response rate and progression-free survival.

3. PATIENT SELECTION

3.1 Eligibility Criteria

For questions concerning patient eligibility, please contact the study team via email at ETCTN10405@upmc.edu. Pre-treatment dental evaluation is recommended for patients who are not edentulous.

- 3.1.1 Patients must have histologically confirmed recurrent or metachronous (second primary) unresectable head and neck squamous cell carcinoma, including oral cavity, oropharynx, larynx, hypopharynx, cutaneous, salivary gland, paranasal sinus, or cervical lymphadenopathy (head and neck cancer of unknown primary). **Core needle biopsy (preferably at least three 18-gauge cores) or incisional biopsy is preferred over FNA for diagnosis of recurrent disease or new primary head and neck squamous cell carcinoma to provide sufficient tumor tissue for correlative studies.** Unresectable refers both to patients who have declined surgery and patients deemed unresectable by otolaryngology. This includes patients for whom curative resection is medically contraindicated and/or would be associated with excessive surgical risk (as deemed by the consulting otolaryngologist) or undue surgical morbidity (*e.g.*, total glossectomy, laryngectomy, and/or major resection requiring free flap reconstruction).
- 3.1.2 Patients must have either recurrent disease or a new primary squamous cell carcinoma of the head and neck within a previously irradiated area (radiotherapy to dose ≥ 40 Gy, *i.e.*, in-field recurrence).
- 3.1.3 Patients must have completed prior radiotherapy ≥ 6 months prior to enrollment.
- 3.1.4 Patients must meet at least one of the following criteria: 1) received prior platinum-containing chemotherapy; and/or 2) tumor expresses PD-L1 (Combined Positive Score [CPS] ≥ 1).
- 3.1.5 Patients who have received anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy must have had disease progression while on this therapy. Patients who have not received prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy are also eligible.
- 3.1.6 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of BAY 1895344 with pembrolizumab in patients < 18 years of age, children are excluded from this study.
- 3.1.7 ECOG performance status ≤ 2 (Karnofsky $\geq 50\%$, see Appendix A) and a life expectancy of ≥ 3 months.
- 3.1.8 Patients must have adequate organ and marrow function as defined below:
- leukocytes $\geq 3,000/\text{mcL}$

- absolute neutrophil count $\geq 1,500/\text{mcL}$
- platelets $\geq 100,000/\text{mcL}$
- hemoglobin $\geq 9 \text{ g/dL}$ or 5.6 mmol/L without transfusion or erythropoietin dependency (within 7 days of assessment)
- total bilirubin $\leq 1.5 \times$ institutional upper limit of normal (ULN)
(If total bilirubin $> 1.5 \times$ ULN, direct bilirubin must be $< \text{ULN}$)
- AST(SGOT)/ALT(SGPT) $\leq 2.5 \times$ institutional ULN ($\leq 5 \times$ ULN for patients with liver metastases)
- Creatinine OR measured or calculated or calculated creatinine clearance (CrCl)^a $< 1.5 \times$ institutional ULN OR
- glomerular filtration rate (GFR) $> 60 \text{ mL/min/1.73 m}^2$ (see Appendix B)
- albumin $> 2.5 \text{ mg/dL}$
- International normalized ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
- Activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

^aCrCl should be calculated per institutional standard.

- 3.1.9 Patients must have measurable disease (at least one measurable lesion) as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. **Baseline imaging must include neck CT (preferably contrast-enhanced) and chest CT or skullbase to midthigh PET/CT (preferably with contrast-enhanced neck CT if diagnostic contrast-enhanced neck CT not available).** Patients who have undergone surgery aside from biopsy may be included if gross disease is present within the surgical resection bed or at another site.
- 3.1.10 Patients must have no contraindications to pembrolizumab, including no history of organ allograft transplantation or active autoimmune disease (active defined as having autoimmune disease-related symptoms and detectable autoantibodies) that has required systemic treatment in the past 2 years (*i.e.*, use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (*e.g.*, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, *etc.*) is not considered a form of systemic treatment.
- 3.1.11 Human immunodeficiency virus (HIV)-infected patients may participate IF they meet the following eligibility requirements:
- They must be stable on their anti-retroviral regimen, and they must be healthy

- from an HIV perspective.
 - They must have a CD4 count of greater than 250 cells/mcL.
 - They must not be receiving prophylactic therapy for an opportunistic infection.
- 3.1.12 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy (*e.g.*, not HBsAg reactive), if indicated.
- 3.1.13 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load (*e.g.*, HCV RNA [qualitative] is not detected).
- 3.1.14 Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging using the identical imaging modality for each assessment, either magnetic resonance imaging [MRI] or computed tomography [CT] scan, for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
- 3.1.15 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial (*e.g.* basal cell carcinoma, early-stage differentiated thyroid carcinoma, low-risk prostate cancer, ductal carcinoma in situ of the breast, squamous cell carcinoma of the skin that has undergone potentially curative therapy, *in situ* cervical cancer). Patients with 10 or fewer distant metastases may be eligible for this trial if they meet performance status inclusion criteria.
- 3.1.16 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
- 3.1.17 Enrolling site must perform PD-L1 testing on tumor biopsy per institutional protocol (local testing or tissue sent to outside laboratory for PD-L1 IHC 22C3 pharmDx). Combined positive score (CPS) is recommended for PD-L1 scoring. Test result does not need to be available at the time of enrollment and treatment initiation, unless the patient has not received prior platinum-containing chemotherapy. For patients without a history of platinum-containing chemotherapy, PD-L1 testing with $CPS \geq 1$ is required to be eligible to receive pembrolizumab.
- 3.1.18 Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

The effects of BAY 1895344 on the developing human fetus are unknown. For this reason and because DNA-damage response inhibitors as well as other therapeutic agents

used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception as outlined in Section 6.8 prior to study entry, for the duration of study participation, and for 6 months after completion of BAY 1895344 therapy or 4 months after completion of pembrolizumab therapy, whichever is later. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of BAY 1895344 therapy or 4 months after completion of pembrolizumab therapy, whichever is later. See Section 6.8 for definitions of females and males of childbearing potential and adequate methods of contraception.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the patient.

- 3.1.19 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

- 3.2.1 Patients who are unable to take oral medications.
- 3.2.2 Patients with, nasopharyngeal carcinoma, paranasal sinus cancers with histology other than squamous cell carcinoma, or salivary gland cancers with histology other than [squamous cell carcinoma](#).
- 3.2.3 Patients who have had more than one prior course of head and neck radiotherapy.
- 3.2.4 Patients who have disease surrounding $\geq 180^\circ$ of the carotid artery.
- 3.2.5 Patients with gross tumor involvement of the mandible.
- 3.2.6 Patients with widely metastatic disease.

Note: Patients with oligometastatic disease (defined as ten or fewer distant metastases) may qualify for the study.

- 3.2.7 Patients who have had chemotherapy, targeted small-molecule therapy, or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

Note: Patients with $\leq$ Grade 2 neuropathy or $\leq$ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If patients received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

- 3.2.8 Patients who are currently participating and receiving study therapy or have participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
- 3.2.9 Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 4 weeks prior to initiating the study drug BAY 1895344.
- 3.2.10 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI.
- 3.2.11 Has had a prior monoclonal antibody other than anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy within 4 weeks prior to study Day 1 or who has not recovered (*i.e.*, $\leq$ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
Note: Patients who received anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy within 4 weeks prior to study initiation are eligible if they have exhibited disease expression while on this therapy.
- 3.2.12 Has new or progressive brain metastases, or leptomeningeal disease.
- 3.2.13 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, *in situ* cervical cancer, ductal carcinoma in situ of the breast, early-stage differentiated thyroid cancer, or low-risk prostate cancer.
Note: As discussed above (Sections 3.1.15 and 3.2.7), patients with limited metastatic disease (10 or fewer distant metastases) may qualify for the study.
- 3.2.14 Patients with carcinomatous meningitis should be excluded.
- 3.2.15 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BAY 1893544 or pembrolizumab.
- 3.2.16 Has an active autoimmune disease that has required systemic treatment in the past 2 years (*i.e.*, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (*e.g.*, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, *etc.*) is not considered a form of systemic treatment.

- 3.2.17 Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- 3.2.18 Patients whose disease has improved or remained stable (no evidence of disease progression) while receiving therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent are ineligible.
- 3.2.19 Patients receiving any medications that are substrates of CYP3A4 with a narrow therapeutic window, or strong inhibitors/inducers of CYP3A4 are ineligible, if they cannot be transferred to alternative medication. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Appendix C should be presented to the patient.
- 3.2.20 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, interstitial lung disease or active, non-infectious pneumonitis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.21 Patients with psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.22 Pregnant women are excluded from this study because BAY 1895344 as a DNA-damage response inhibitor may have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with BAY 1895344, breastfeeding should be discontinued if the mother is treated with BAY 1895344 and for 4 months after the end of BAY 1895344 treatment. These potential risks may also apply to other agents used in this study.
- See Section 6.8 for information on contraception and pregnancy.
- 3.2.23 Has a known history of active tuberculosis (TB).
- 3.2.24 Has received a live vaccine within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted. Similarly, COVID-19 vaccines are permitted.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate

with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see <http://grants.nih.gov/grants/funding/phs398/phs398.pdf>.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at <https://ctepcore.nci.nih.gov/rcr/>. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR): MD, DO, or international equivalent,
- Non Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- Associate Plus (AP): clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		

Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN,
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the [NCI RCR](#) page on the [CTEP website](#) for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.cocccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record.

- Have an active CTEP status,
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster,

- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (<https://www.ctsuo.org>)
- Click on *Protocols* in the upper left of the screen
 - Enter the protocol number in the search field at the top of the protocol tree, or
 - Click on the By Lead Organization folder to expand, then select LAO-PA015 and protocol number 10405.

Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements For P10405 Site Registration

- A Study Initiation Visit (SIV) or Site Initiation Teleconference (SIT) is required for each participating site prior to activation. The local site PI must participate on the call. To schedule a SIV or SIT, please email the study team email listed on the front page of the protocol.
- RT-Specific Pre-Registration Requirements

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the IROC Houston QA Center will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

Credentialing Requirements	Web Link for Procedures and Instructions: [www.irochouston.meanderson.org]	
	Treatment Modality	Key Information
	Photons	
Facility Questionnaire	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	✓	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation	✓	An IMRT Head and Neck phantom irradiation provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that an institution, depending on its treatment delivery modalities, may be required to irradiate a phantom on different delivery machines such as TomoTherapy and CyberKnife.
IGRT Verification Study	✓	Institutions must be credentialed for boney anatomy IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Credentialing Issued to:		
Institution	✓	IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

- Specimen Tracking System Training Requirement:
 - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
 - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
 - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time

- This training will need to be completed before the first patient enrollment at a given site.

Please contact STS Support at Theradex for the training (STS.Support@theradex.com).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements as well as include a Master Task List.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the members' side of the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
 - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at <https://open.ctsuh.org> or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at <https://www.ctsuh.org> or <https://open.ctsuh.org>. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsuhcontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation

System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

- Availability of a pre-treatment tissue specimen for correlative studies must be confirmed by site staff before enrollment.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: “Rave CRA” and “Rave CRA (Labadmin)” for data entry at the treating institutions and “Biorepository” for users receiving the specimens for processing and storage at reference labs and the Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on the use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at <https://www.ctsuo.org> or at <https://open.ctsuo.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsuocontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 **General Guidelines**

Following registration, patients should begin protocol treatment within 21 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient’s registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	- Formalin-fixed paraffin-embedded (FFPE) tumor tissue block¹ from recurrence/second primary (strongly preferred) If archival tumor tissue block is not available, then submit: 1 H&E-stained slide (3-5 micron)¹ 15-20 (10-micron) unstained uncharged slides¹	EET Biobank
	Freshly cut FFPE slides from archival tissue (recurrent tumor biopsy or new primary tumor biopsy) per institutional guidance for PD-L1 testing (mandatory) Note: Redacted pathology report with PD-L1 test results (preferably Combined Positive Score [CPS]) is acceptable	Local testing (PD-L1 IHC 22C3 pharmDx or SP263)
Baseline		
	20 mL whole blood in Streck cfDNA tubes (mandatory)	EET Biobank
	2 × 8.5 mL blood in yellow-top ACDA tube (mandatory)	Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center
Week 2		
	2 × 8.5 mL blood in yellow-top ACDA tube (mandatory)	Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center
Week 5		
	2 × 8.5 mL blood in yellow-top ACDA tube (mandatory)	Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center
6 Months		
	2 × 8.5 mL blood in yellow-top ACDA tube (mandatory)	Cancer Pharmacokinetics and Pharmacodynamics

		Facility at UPMC Hillman Cancer Center
12 Months		
	2 × 8.5 mL blood in yellow-top ACDA tube (mandatory)	Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center
Disease Progression		
	20 mL whole blood in Streck cfDNA tubes (optional)	EET Biobank
¹ For archival tissue, a copy of the corresponding anatomic pathology report labeled with the Patient Study ID and Universal Patient ID must be sent with the tissue and uploaded to Rave. If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 21). Note: Insufficient archival tissue for correlative studies does not preclude patient enrollment.		

5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

N/A

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

Kits for the collection and shipment of blood in Streck cfDNA tubes to the EET Biobank can be ordered online via the Kit Management system: (<https://kits.bpc-apps.nchri.org/Auth/Login>).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kits per kit type per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the Biobank. Institutional supplies must be used for all other specimen collection and processing.

5.3.2 Scheduling of Specimen Collections

5.3.2.1 Scheduling of Specimen Collections for the EET Biobank

Please adhere to the following guidelines when scheduling procedures to collect samples:

- Archival (FFPE) tissue may be shipped on Monday through Thursday.
- Fresh blood specimens may be collected and shipped Monday through Friday.

5.3.2.2 Scheduling of Specimen Collections for the Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center

Blood in ACDA tubes may be collected and shipped Priority Overnight on the day of collection on Monday through Thursday.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
 - Institution and affiliate name
 - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
 - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

5.4.2.2 Tissue Specimen Labels

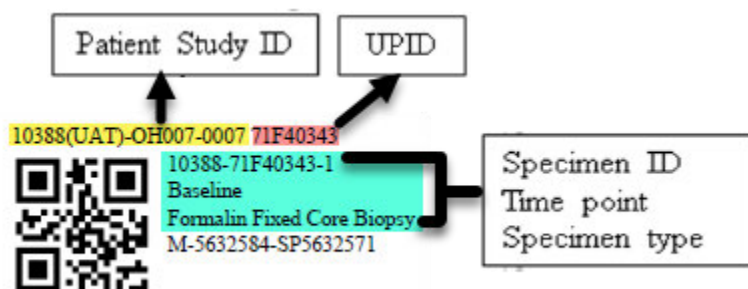
Include the following on all tissue specimens or containers:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic, or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: <https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/>

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time.

The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and time on each label. After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number, diagnosis, or relevant dates (such as collection date), and include the UPID and patient study ID on each document (either by adding a label or hand-writing).

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status**.

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click “Send Email Alert” checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Specimen Collection

5.5.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
 - Surface area: 25 mm² is optimal. Minimum is 5 mm².
 - Volume: 1 mm³ optimal. Minimum volume is 0.2 mm³, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:

- One H&E-stained slide (3-5 micron)
- Fifteen to twenty (15-20) 10-micron unstained air-dried uncharged slides

Process and number slides sequentially.

See Section 5.4.2 for labeling instructions.

5.5.2 Collection of Blood in ACDA Tubes for Shipping Whole Blood

1. Label two ACDA anti-coagulated Vacutainer tubes (yellow tops; BD Vacutainer ACD Solution A, Reference # 364606) per timepoint according to the instructions in Section 5.4.2.
2. Collect 8.5 mL blood into each ACDA tube.
3. Tubes should remain at room temperature. Please note that refrigeration or storage on ice will limit the ability to recover PBMCs.
4. Ship tubes overnight to the Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC on the day of collection (whenever possible) according to the instructions in Section 5.7.

5.5.3 Collection of Blood in Streck cfDNA Tube

1. Label two 10-mL Streck cfDNA tubes according to the instructions in Section 5.4.2.

2. Collect 20 mL of blood into the pre-labeled tubes and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. For patients with an indwelling catheter: heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as a first choice collection method. If a Streck cfDNA tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT is recommended.
3. **After collection, blood in Streck cfDNA tubes should never be refrigerated**, as this will compromise the specimen. Blood collected in Streck cfDNA tubes is stable at room temperature.

5.6 Shipping Specimens from Clinical Site to the EET Biobank

5.6.1 General Shipping Information

When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be sent to the EET Biobank as soon as possible and uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

5.6.1.1 Required Forms for Tissue Submissions:

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	Required Forms
Archival	1. Shipping List 2. Corresponding Pathology Report
Whole Blood in Streck cfDNA tubes	1. Shipping List

5.6.2 Specimen Shipping Instructions

Archival (FFPE) tissue may be shipped on Monday through Thursday.

Fresh blood may be shipped on Monday through Friday. Please select “Saturday Delivery” when shipping fresh blood on a Friday.

5.6.2.1 Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.4.2.2.
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimen. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.
4. Include a copy of the forms listed above and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.2 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in Section 5.4.2.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. **Note:** If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. **Do not refrigerate, freeze, or microwave.**
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank

The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

5.6.4 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

5.7 Shipping of Specimens from Clinical Site to Other Laboratories

5.7.1 Shipping of Specimens to UPMC

5.7.1.1 Specimen Shipping Instructions

Blood samples will be collected at the time points specified in Section 5.1. Tubes should remain at room temperature. Please note that refrigeration or storage on ice will limit the ability to recover PBMCs. Completed PBMCs Blood Samples Requisition Form (Appendix F) should be uploaded into Rave before shipping, and a copy will be included in the envelope. Samples should be shipped overnight to the Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center.

- Ship samples on the same day as collection. To maintain patient confidentiality, the patient's name must not appear on the FedEx label or on the outside of the shipping package.
- Place ACDA tubes for PBMCs in zip-lock bags.
- Place zip-lock bags in Biohazard envelope with absorbent material. Expel excess air from Biohazard envelope before sealing. Place biohazard envelope in Tyvek envelope. Expel excess air from Tyvek before sealing. If shipping specimens for multiple participants, please ensure that the samples are distinctly labeled and placed in separate zip-lock bags to avoid specimen confusion. Place the specimen bag(s) along with the PBMCs Blood Samples Requisition Form (Appendix F) in shipping container, close and secure with tape.
- Affix the FedEx airbill to the outside of the shipping container.

- Place Category B, UN3373 label to outside of shipping container.
- Ship all samples at room temperature by FedEx Express Priority overnight. Samples can be shipped Monday through Thursday. Note that samples **cannot** be shipped on Fridays or the day prior to federal holidays.
- Prior to shipping all blood samples, please notify the lab of a scheduled shipment by email at PITT-PK@upmc.edu or telephone (412-623-3248) at least 24 hours prior to shipment.

5.7.1.2 Shipping Address

Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC Hillman Cancer Center
Room G28 Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213

5.7.1.3 Contact Information for Assistance

Lab phone: 412-623-3248
Lab fax: 412-623-1212
Lab email: PITT-PK@upmc.edu
Lab director email: beumerjh@upmc.edu

5.8 Biomarker Plan

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	Whole exome sequencing (WES)	NGS CLIA: N	Integrated To determine whether certain gene mutation signatures (impaired DDR) predict sensitivity to the treatment	DNA from FFPE slides Slides or block acceptable	Archival	M	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov
2	PD-L1 expression	IHC (Dako) CLIA: N	Exploratory Association of PD-L1 expression with overall response rate and progression-free survival	Unstained slides from FFPE tissue	Archival	M	Local testing Redacted PD-L1 report acceptable, preferably Combined Positive Score (CPS)
Blood-based Biomarkers							
1	Whole exome sequencing (WES)	NGS CLIA: N	Integrated Germline control	DNA from blood in Streck cfDNA tube	Baseline Collected as part of ctDNA biomarker	M	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
2	ctDNA sequencing	NGS CLIA: N	Integrated Analysis of DNA damage response-related genes	Plasma from blood in Streck cfDNA tube	Baseline Disease progression	M O	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich, Ph.D. chris.karlovich@nih.gov
3	Peripheral blood mononuclear cells	Flow cytometry CLIA: N	Exploratory Correlate changes in circulating immune cell populations (<i>e.g.</i> , PD-1 ⁺ Ki67 ⁺ CD8 ⁺ T cells) with overall response rate and progression-free survival	Peripheral blood in yellow-top ACDA tubes	Baseline Week 2 Week 5 6 months 12 months	M	UPMC Hillman Cancer Center/Mowery Laboratory Yvonne Mowery, MD, PhD yvm3@pitt.edu

5.9 Integrated Correlative Studies

5.9.1 Whole Exome Sequencing

5.9.1.1 Specimen Receipt and Processing at the EET Biobank

All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide, and for nucleic acid extractions, additional RNase-free slides. All H&E stained slides will undergo a pathology QA review and annotation for macrodissection. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA will be shipped to the central sequencing laboratory for analysis.

DNA will be extracted from blood collected in Streck cfDNA tubes at baseline following whole blood processing. DNA will be quantitated and stored in a -80°C freezer until shipping for analysis.

5.9.1.2 Site(s) Performing Correlative Study

WES will be performed at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.9.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to the following laboratory:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.9.1.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplerceiving@nih.gov)

5.9.2 ctDNA Sequencing

5.9.2.1 Specimen Receipt and Processing at the EET Biobank

Whole blood collected in Streck cfDNA tubes will be centrifuged to separate plasma. Following plasma processing, DNA will be processed from blood at baseline. At disease progression, plasma and buffy coat will be processed and stored. Plasma and buffy coat aliquots will be stored in a -80°C freezer.

5.9.2.2 Site(s) Performing Correlative Study

ctDNA sequencing will be performed at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.9.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to the following laboratory: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)

1050 Boyles St.

Bldg. 459, Rm. 125

Frederick, MD 21702

Attn: Alyssa Chapman or Ruth Thornton

5.9.2.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 PD-L1 Expression

5.10.1.1 Specimen Receipt and Processing at Local Laboratories

PD-L1 expression analysis will be performed according to local institutional SOPs.

5.10.1.2 Sites Performing Correlative Study

PD-L1 expression analysis will be performed by local laboratories or sent for commercial analysis if the local laboratory does not have the capacity to perform this analysis.

5.10.1.3 Contact Information for Notification of Specimen Shipment

N/A

5.10.2 Peripheral Blood Mononuclear Cells

5.10.2.1 Specimen Receipt and Processing at the Cancer Pharmacokinetics and Pharmacodynamics Facility at UPMC Hillman Cancer Center

PBMCs will be isolated and viably cryopreserved until subsequent processing, which will entail staining with fluorescently labeled antibodies followed by analysis on the BD SORP LSRFortessa, capable of 18 colors.

5.10.2.2 Site Performing Correlative Study

PBMCs will be analyzed in the laboratory of Dr. Yvonne Mowery at UPMC Hillman Cancer Center.

5.10.2.3 Contact Information for Notification of Specimen Shipment

See Section 5.7.1.

5.11 Special Studies

5.11.1 Quality of Life Assessment

5.11.1.1 Outcome Measure

The outcome measure is the Functional Assessment of Cancer Therapy for Patients With Head and Neck Cancer (FACT-H&N), version 4. The FACT-H&N consists of statements rated on a 5-point scale (0-4) to indicate the presence and severity of symptoms and impacts on patients' lives. A 0 on the scale represents "Not at all" and a 4 represents "Very much". Each statement is assessed by the patient as it applies to the previous 7 days. Statements to be assessed are grouped into "Physical Well-Being", "Social/Family Well-Being", "Emotional Well-Being", "Functional Well-Being", and "Additional Concerns".

5.11.1.2 Assessment

5.11.1.2.1 Method of Assessment

The FACT-H&N (Appendix E) will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report.

5.11.1.2.2 Timing of Assessment

Patients will complete the FACT-H&N at baseline and at 3, 6, and 12 months after initiation of study treatment.

5.11.1.3 Data Recording

5.11.1.3.1 Method of Recording

For each patient and time point, a copy of the completed FACT-H&N questionnaire will be uploaded into Rave. Questionnaires will be scored locally, and the score at each time point will be entered into the study database.

5.11.1.3.2 Timing of Recording

The FACT-H&N score will be entered into the database within 30 days of completion.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Pembrolizumab will be administered intravenously every three weeks at a dose of 200 mg per cycle starting on day 1. BAY 1895344 will be administered orally every 12 hours for 3 days on then 4 days off for two weeks, starting on day 7 (i.e., six days after the first dose of pembrolizumab). The BAY 1895344 dose during this lead-in phase prior to initiating SBRT will be 30 mg twice a day, selected based on preliminary results of the ongoing phase 1 clinical trial that is evaluating this combination (NCT04095273). Patients will be imaged by CT (with intravenous contrast, if there are no contraindications) in a thermoplastic immobilization device for radiation treatment planning prior to initiating therapy. Radiation treatment planning and quality assurance will be performed during the first cycle of pembrolizumab with BAY 1895344. SBRT will then be initiated at 1-7 days after the second dose of pembrolizumab (Cycle 2 Days 2-8). SBRT dosing will be 7 Gy x 3 fractions or 8 Gy x 3 fractions, with at least two days between radiotherapy fractions. BAY 1895344 (10 mg, 20 mg, or 30 mg) will be administered orally every 12 hours for 3 doses surrounding each fraction of radiation therapy, with the first dose corresponding to each fraction to be administered at least 1 hour prior to radiation therapy and no more than 6 hours prior to radiation therapy. Given that there are three fractions of radiation therapy, a total of nine doses of BAY 1895344 will be administered during Cycle 2. **Table 1** describes the dose levels for escalation of the BAY 1895344 + SBRT combination treatment. Upon SBRT completion, BAY 1895344 will be discontinued.

Any subsequent oncologic therapies will be documented in the Medidata Rave database. Pembrolizumab or other anti-PD-1 therapy may be continued at the discretion of the treating oncologist. The number of cycles of anti-PD-1/anti-PD-L1 therapy administered after the two pembrolizumab cycles delivered concurrently with BAY 1895344 on trial will be recorded in the Medidata Rave database. For patients with indications for radiation therapy to additional sites outside the head and neck, radiotherapy must be performed either before initiation of study therapy or after the two cycles of pembrolizumab with concurrent BAY 1895344 have been completed (at least 2 weeks after final dose of BAY 1895344). Radiation dose fractionation at the discretion of the treating radiation oncologists. Data on the site(s), dosing, and timing of radiation therapy to other sites will be recorded in the Medidata Rave database.

Table 1. Dose levels of BAY 1895344 + SBRT combination treatment

Dose Level	B1 (BAY)	B2 (BAY)	B3 (BAY)
A1 (SBRT)	7 Gy x 3 fractions 10 mg Q12H x 3 doses with each	7 Gy x 3 fractions 20 mg Q12H x 3 doses with each	7 Gy x 3 fractions 30 mg Q12H x 3 doses with each

	fraction	fraction	fraction
A2 (SBRT)	8 Gy x 3 fractions 10 mg Q12H x 3 doses with each fraction (STARTING DOSE)	8 Gy x 3 fractions 20 mg Q12H x 3 doses with each fraction	8 Gy x 3 fractions 30 mg Q12H x 3 doses with each fraction

Regimen Description

Agent	Dose	Route	Schedule	Cycle Length
BAY 1895344	Cycle 1: 30 mg Cycle 2: Dose as assigned	PO	Q12H Cycle 1: starting Day 7 (3 days on/4 days off) x 2 weeks Cycle 2: Q12H for 3 doses surrounding each SBRT fraction, administered within 1-6 hours before each fraction	21 days
Pembrolizumab	200 mg	IV	D1 of each cycle	21 days
SBRT	Dose as assigned		Cycle 2: Starting between Days 2-8; 3 fractions with at least 2 days without radiation therapy and no more than 3 days without radiation therapy between fractions, e.g. Monday/Thursday/Monday	21 days

6.1.1 CTEP IND Agent

6.1.1.1 BAY 1895344

BAY 1895344 tablets should be taken at least one (1) hour before or two (2) hours after a meal with approximately 240 mL of water.

If a patient vomits after taking study medication, the patient should be instructed not to retake the dose and should take the next dose as originally scheduled.

Patients will be requested to maintain a daily medication diary of each dose of BAY 1895344 (Appendix D). The medication diary will be returned to the clinic staff at the end of each cycle.

6.1.2 Commercial Agent

6.1.2.1 Pembrolizumab

Trial treatment of pembrolizumab will be administered on Day 1 of each 3-week treatment cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Note: Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (*i.e.*, elective surgery, unrelated medical events, patient vacation, holidays) not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record. If Cycle 2 of pembrolizumab is held for up to 3 weeks, then BAY 1895344 and radiation therapy will also be held until after Cycle 2 of pembrolizumab has been administered.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2-micron to 5-micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line. Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 30 minutes, -5 min/+10 min).

6.1.3 Stereotactic Body Radiation Therapy (SBRT)

6.1.3.1 Definition of Stereotactic Body Radiation Therapy Targeting and Treatment

For the purposes of this protocol, the term 'stereotactic body radiation therapy' (SBRT) implies the targeting, planning, and aiming of radiation beams along any trajectory in three-dimensional (3-D) space toward a target of known 3-D coordinates. Given that fiducials are not required for image guidance, volumetric image-based guidance (cone beam CT, CT-on-rail, or MRI on an MR-Linac) with approval by an attending radiation oncologist is required to confirm appropriate target location before each fraction of radiation therapy is delivered.

6.1.3.2 Stereotactic Body Radiation Therapy Prescription

SBRT will be administered in 3 fractions with at least 2 days without radiation therapy and no more than 3 days without radiation therapy between each fraction. For example, potential SBRT schedules would include Monday/Thursday/Monday, Monday/Friday/Monday, Monday/Friday/Tuesday, Tuesday/Friday/Monday, and Tuesday/Friday/Tuesday. The prescription dose per fraction is 700 or 800 cGy (7 or 8 Gy), depending on the dose level assigned. The total prescription dose is 2,100 or 2,400 cGy (21 or 24 Gy), depending on the assigned dose level. SBRT is scheduled on trial between Day 22 to Day 35 of the study.

6.1.3.3 Technical Factors

6.1.3.3.1 Physical Factors

Only photon (x-ray) beams with photon energies less than or equal to 10 MV are allowed. Cobalt-60 or charged particle beams (including electrons, proton, and heavier ions) are not allowed on this protocol.

Most commercially available photon-producing treatment platforms are allowed. Conventional linear accelerators or specialized linear accelerators with image guidance (*e.g.*, Novalis, Trilogy, Synergy, Artiste, TrueBeam) are allowed. These units can be used with conformal dose delivery,

intensity-modulated radiation therapy (IMRT). Specialized dose-painting accelerators (Cyberknife, or Tomotherapy) are allowed provided that the units meet the technical specifications of the protocol and are used in a fashion that passes any credentialing required by the protocol. Conventional linear accelerators without add-on image-guided radiation therapy (IGRT) must have some other 3-dimensional IGRT capability such as computed tomography (CT)-on-rails in the treatment room.

3-D conventional radiation therapy (3-DCRT) or IMRT (including volumetric-modulated arc therapy [VMAT]) are all acceptable planning techniques.

6.1.3.3.2 Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of three centimeters (3 cm) is required for any field used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the planning tumor volume is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions (<2.0 cm axial, <1.0 cm craniocaudal gross tumor volume dimension). If field size smaller than 3×3 cm is used, then quality assurance of the treatment planning system must be performed and deemed acceptable by IROC. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume. For sites using dose painting including IMRT techniques where, by design, the entire planning tumor volume is not encompassed for each beam, smaller beam apertures are allowed.

6.1.3.3.3 Fiducial Placement

N/A

6.1.3.3.4 Patient Positioning

Patients will be positioned in a stable position for accurate reproducibility of the target position during treatment and between treatments. Positions uncomfortable for the patient should be avoided so as to minimize uncontrolled movement during treatment. Immobilization must be reliable to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV). Positioning patients on flat couches without a rigid pillow or frame and relying solely on image-guidance for reproducible set-up is strongly discouraged. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides with reference to the stereotactic coordinate system or a thermoplastic mask.

6.1.3.3.5 Respiratory Motion Assessment and Management

N/A

6.1.3.3.6 Simulation and Planning

The patient will undergo a treatment planning simulation (after fiducial placement if applicable, per institutional practice). In order to improve visualization of the anatomy, the patient should be given intravenous contrast unless there are contraindications (*e.g.*, renal insufficiency, allergy to contrast) per institutional practice guidelines. All patients will be immobilized using a thermoplastic mask per institutional routine in order to prevent any inadvertent patient motion during SBRT treatment.

All patients must undergo CT-based treatment planning in custom-made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used) and be adequate to ensure contouring of all targeted cancers, as well as necessary organs at risk (OAR), as defined below. High-resolution CT scans should be obtained with uniform slice thickness of less than or equal to three millimeters (≤ 3 mm). Intravenous contrast may be used at the discretion of the treating physician. Vascular contrast from the planning dataset is recommended to be converted to water equivalent density if used for treatment planning. Datasets without intravenous contrast may be used for dose calculation. Triphasic CT scan is recommended to aid in identification of the irradiation lesion(s).

The target lesion will be outlined by an appropriately trained physician and designated the gross tumor volume (GTV). More than one site within the head and neck region can be treated, and non-contiguous target volumes are permitted. For example, multiple separate involved lymph nodes and a non-adjacent primary tumor recurrence site can be treated as GTV. For patients who have undergone incomplete surgical resection with gross residual disease, inclusion of the surgical bed within the target volume will be at the discretion of the treating radiation oncologist. The target will generally be drawn using CT abdominal window and soft tissue windows with contrast (aided by additional diagnostic imaging studies as needed [PET/CT or MRI]). This target will not be enlarged (*i.e.*, the GTV and the clinical target volume [CTV] are identical [GTV=CTV]). An additional two millimeters (2 mm) should be added in all planes to the GTV to constitute a planning target volume (PTV).

6.1.3.4 SBRT Treatment Planning Technique

6.1.3.4.1 Planning Parameters

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, nine (9) or more beams of radiation will be used with roughly equal weighting. In general, large lesion size requires more treatment beams. When static beams are used, a minimum of seven non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (*i.e.*, no additional "margin" for dose buildup at the edges of the blocks or multi-leaf collimator jaws beyond the PTV). The only exception will be when observing the minimum field dimension of three centimeters (3cm) when treating small lesions. Prescription lines covering the PTV will typically range between 60-90% line (rather than 95-100% as is common with conventional radiotherapy); however, higher isodose line hotspots must be manipulated to occur within the

target and not in adjacent normal tissue.

6.1.3.4.2 Heterogeneity Correction

All institutions must use IROC-approved heterogeneity correction algorithms:

[http://irochouston.mdanderson.org/RPC/Services/Anthropomorphic %20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf](http://irochouston.mdanderson.org/RPC/Services/Anthropomorphic%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf)

6.1.3.4.3 SBRT Planning Definitions

Normalization: The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.

Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be $\geq 60\%$ and $\leq 90\%$ of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted above.

Target Dose Heterogeneity: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR.

Critical Organ Doses: Respect all critical organ dose-volume limits listed below.

High-Dose Spillage:

a. *Location:* Any dose $>105\%$ of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.

b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.

c. The ratio of the prescription isodose volume to the PTV volume should be <1.2 . Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_prescription (*i.e.*, V_5000, V_4800, V_5400) with the prescription changing to reflect the prescription dose in cGy.

d. Elliptically shaped tumor may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected.

e. These criteria will not be required in treating very small tumors (<2.5 cm axial GTV dimension or <1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm (see Section 6.1.3.3.2) results in the inability to meet a conformity ratio of 1.5.

Planning Priorities: Every attempt should be made to successfully satisfy all of the planning goals and OAR criteria without deviation. In some circumstances, it may not be possible to meet all the ideal criteria leading to plans with an acceptable deviation. Thus, suggested priority of planning goals in order of importance is (1) respect spinal cord, brainstem, and brachial plexus dose constraints; (2) meet dose “compactness” constraints including the prescription isodose surface coverage, high dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50%) as these define the “essence” of SBRT (dose compactness should be assessed for plans based on treatment dose for a single lesion at a time); (3) meet critical structure constraints other than those listed in item #1 as the OAR constraints are last in priority (except for nervous system tolerance) and as an example, in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation even at the expense of a non-spinal cord normal tissue having acceptable deviation; (4) unacceptable deviations should be avoided in all cases; and (5) in cases where PTV coverage cannot be achieved while avoiding unacceptable deviations to OAR, coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose only in this clinical situation.

Organs at Risk (OAR): Protocol-specific OARs contoured depend on the location of cancers to be treated. In general, an OAR within three (3 cm) of the PTV should be contoured and might include the following structures:

Structure Description	Standard Name
Lungs, left/right	Lung L, Lung R
Lungs, combined	Lungs
Heart	Heart
Great vessels	GreatVes
Esophagus	Esophagus
Pharynx	Pharynx
Spinal cord	SpinalCord
Brain	Brain
Brainstem	Brainstem
Carotid arteries	A_Carotid_L, A_Carotid_R
Parotid glands	Parotid_L, Parotid_R
Submandibular glands	GlnD_Submand_L, GlnD_Submand_R
Larynx	Larynx
Oral cavity	OralCavity
Mandible	Mandible
Skin	Skin

Contouring of Normal Tissue Structures: In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as follows:

Brain

The brain will be contoured as one complete structure within the cranial vault.

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal ending at L2. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. It is not necessary for the entire lungs to be in the planning scan.

Oral Cavity

The oral cavity will be defined as a composite structure consisting of the anterior 1/2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands

Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. The retromandibular vein is included in the contour. Left and right parotid glands should be contoured as separate structures.

Submandibular glands

Submandibular glands will be defined in their entirety based on the treatment planning CT scan. Left and right submandibular glands should be contoured as separate structures.

Pharynx

This will be defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles (approximately 3 mm). This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

Larynx

This will be defined as a “triangular prism shaped” volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis. For patients who have had a total laryngectomy, this structure is not applicable.

Brachial Plexus

This will be contoured as the ventral rami from C5 (exiting at C4-C5) through T1 (exiting at T1-T2) as they exit through the neural foramina joining to form the trunks extending through the space between the anterior and middle scalene muscles. At the level where the scalene muscles insert into the first rib, the major trunks of the brachial plexus should follow the subclavian artery into the axilla. For more detailed step-by-step instructions, refer to Truong *et al.*, *Radiographics* 2010 (<https://pubs.rsna.org/doi/full/10.1148/rg.304095105>). The left and right brachial plexuses should be contoured as separate structures.

Mandible

This includes the entire boney structure of the mandible from TMJ through the symphysis. Teeth are not included. Contouring should be carried out using bone windows.

Carotid artery

The carotid artery will be defined as the common carotid artery and the internal carotid artery, including the vascular wall and lumen. The right carotid artery contour starts at its origin from the brachiocephalic trunk. The left carotid artery contour starts at its origin from the aortic arch. The upper border will be defined at the level of the sella turcica. The left and right carotid arteries should be contoured as separate structures. Each contour will be uniformly expanded by 2 mm to generate an additional avoidance structure (carotid artery + 2 mm).

Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations

PTV + 2 cm

As part of the QA requirements for “low dose spillage” listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible, this structure should be constructed as a single contour that is 2 cm larger than the PTV.

6.1.3.5 Radiation Dose Constraints

Dose Constraints for SBRT Plan

Structures ^ψ	Goal	Variation Acceptable	Deviation Unacceptable	Avoidance Endpoint
Spinal Cord*	V12Gy <0.035 cc	D _{max} 12.5 Gy	D _{max} <12.5 Gy required	Myelitis
Brainstem*	D _{max} <10 Gy	D _{max} <12 Gy	D _{max} <12 Gy required	Brainstem necrosis

Brachial plexus*	V24Gy <0.035 cc	V22Gy <3cc	V22Gy ≥ 3 cc	Brachial plexopathy
Oral Cavity ^Ω	V24Gy <0.035 cc	V25Gy <1 cc	V25Gy ≥ 1 cc	Soft tissue necrosis
Pharynx ^Ω	V25Gy <0.035 cc	V20Gy <2 cc	V20Gy ≥ 2 cc	Feeding tube dependence
Esophagus	V24Gy <0.035 cc	V15Gy <5 cc	V15Gy ≥ 5 cc	Perforation; feeding tube dependence
Larynx ^Ω	V22Gy <2 cc	V24Gy <2 cc	V24Gy >2 cc	Laryngeal edema; chondronecrosis
Mandible	V22Gy <2 cc	V24Gy <2 cc	V24Gy >2 cc	Osteoradionecrosis
Left carotid artery+2 mm	V22Gy <0.035 cc	V24Gy <0.035 cc	V24Gy ≥ 0.035 cc	Carotid blowout
Right carotid artery+2 mm	V22Gy <0.035 cc	V24Gy <0.035 cc	V24Gy >0.035 cc	Carotid blowout
Lung	V14Gy <750 cc	V14Gy <1,000 cc	V14Gy $\geq 1,000$ cc	Pneumonitis
Skin	V26Gy <0.035 cc	V25Gy <1 cc	V25 ≥ 1 cc	Ulceration
Left cochlea	D _{max} ≤ 12 Gy	D _{max} ≤ 15 Gy	D _{max} >15 Gy	Hearing loss
Right cochlea	D _{max} ≤ 12 Gy	D _{max} ≤ 15 Gy	D _{max} >15 Gy	Hearing loss
Temporal lobe	V20Gy <0.035 cc	V20Gy <2 cc	V20Gy ≥ 2 cc	Temporal lobe necrosis
Target Volume	Goal	Variation Acceptable	Deviation Unacceptable	
PTV	D1cc $\leq 110\%$ D100% $>90\%$	D1cc $\leq 120\%$ D95% $>90\%$	D1cc >120% D95% <90%	
GTV	D _{min} $\geq 95\%$	D _{min} $\geq 90\%$	D _{min} <90%	

^ΩGiven that patients with paranasal sinus or nasopharynx cancers are excluded from enrollment, dose constraints have not been listed for retinas, optic nerves, and optic chiasm. However, these structures will be reviewed during the radiation therapy plan QA process.

*When possible, a plan sum should be generated utilizing the original head and neck radiation treatment plan and the new reirradiation SBRT plan. If the spinal cord, brainstem, and/or brachial plexus maximum doses are available from radiation therapy treatment records but a plan summary cannot be generated, then the prior maximum doses should be utilized to calculate personalized dose constraints that may be stricter than the above table based on equivalent dose in 2-Gy fractions with an alpha/beta of 2 (EQD₂) for each of these normal structures per below:

- **Spinal cord:** EQD₂ D_{max} on plan sum = 50 Gy
 - Calculate EQD₂ D_{max} from initial plan and multiply by dose recovery factor based on time passed since prior radiation therapy (0.75 if 6 to 12 months; 0.67 if >12 but ≤ 24 months; 0.5 if >24 months)
 - Utilize the above adjusted EQD₂ D_{max} from initial plan to account for dose recovery in calculating the EQD₂ D_{max} for plan sum of prior plan and SBRT plan

- **Brainstem:** EQD2₂ D_{max} on plan sum = 55 Gy
- **Brachial Plexus:** EQD2₂ D_{max} on plan sum = 95 Gy if feasible without sacrificing GTV coverage

^Ω For tumors immediately adjacent or involving these structures, the PTV may be subtracted from the organ at risk contour.

6.1.3.6 Online Treatment Image-Guided Localization and Treatment

SBRT image-guided radiation therapy is the delivery of SBRT with online imaging capabilities and verification. This is accomplished with standard treatment planning with position verification using 2-dimensional kilovoltage (KV) images to evaluate the position of the bony anatomy and fiducial markers (if applicable) as well as 3-D cone beam imaging. 3D KV cone beam CT (CBCT) scan is a CT scan taken of the patient and target structure of interest while the patient is immobilized on the treatment table. During the treatment, the patient is immobilized exactly as was done for the simulation. The patient is then set-up in the treatment position according to laser-guiding body tattoos in the treatment room. Live images of the patient are obtained with diagnostic X-ray tubes and amorphous silicon detectors for patient positioning. A therapist will initially obtain a KV image to align the anatomy, followed by a CBCT for image registration based on the location of the adjacent normal tissues, fiducial markers (if applicable), and visible tumor abnormality (if possible) noted in the CT. The patient position is then adjusted to move the patient into the exact position corresponding to the designed treatment plan.

If the patient requires additional repositioning, another set of KV orthogonal images and CBCT will be obtained to confirm tumor localization. Once the latter is confirmed, treatment may be delivered.

All planned SBRT treatment segments will be delivered whenever possible. If SBRT treatment must be terminated prematurely on any fractions of one to three, compensate as follows: If 2/3 or more of all non-zero segments were delivered, then the untreated segments plus the full next fraction should be treated on the next treatment day (this should introduce an error of <5% in biologic effective dose delivered). If fewer than 2/3 of the non-zero segments were treated, then the untreated portion of this fraction (only) will be made up for on the following interval day. If treatment must be terminated prematurely on the third fraction, and 90% of the non-zero segments were treated, then no further treatment shall be given (this should introduce an error of <5% for total biologic effective dose delivered). If fewer than 90% of the non-zero segments were treated, then the deficit shall be delivered on the following day. All such variations shall be recorded.

6.1.3.7 Radiation Plan Quality Assurance (QA)

The radiation therapy plan (RT-DICOM) will be uploaded to IROC for central quality assurance (QA) by Dr. Yvonne Mowery or a qualified radiation oncologist at IROC at least 7 days prior to the radiation therapy start date. When available, a plan sum will also be uploaded, combining the SBRT treatment plan and the original radiation treatment plan. Central QA will be performed within 72 hours to allow sufficient time for treatment plan adjustments to be made and approved

prior to the planned radiation therapy start date, if necessary.

Submission of Digital Radiation Therapy Data

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps (see Section 13.2 for details). Additional information is available at: <https://triadhelp.acr.org/>

Use of SFTP will also be accepted as an alternate method of data submission on this study. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data.

Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

Items to be Submitted at Least 7 Days Prior to the Start of RT

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- If available, a plan sum combining the SBRT treatment plan and the original radiation treatment plan.
- Copies of any imaging studies used to define the target volume.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Dose prescription for the entire treatment.
- RT-1 Dosimetry Summary Form.

Within one week of the completion of radiotherapy, the following data shall be submitted:

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas.
- RT-2 Radiotherapy Total Dose Record Form.
- If there are any changes in the patient's status (*i.e.*, early discontinuation of protocol therapy, delay in starting radiotherapy, or break in radiotherapy), these should be communicated in writing to IROC Rhode Island.

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island QA Center
Phone: (401) 753-7600
Email: physics@qarc.org

6.2 Definition of Dose-Limiting Toxicity

The time period for dose-limiting toxicity (DLT) assessment will start with administration of the first dose of pembrolizumab in Cycle 1 and end at 90 days after the last dose of radiation therapy. Any patient who experiences a DLT during the lead-in (Cycle 1) will not proceed to

Cycle 2 with concurrent SBRT. In this case, the patient would be considered non-evaluable and would not count towards the number of patients treated at the current dose level.

The occurrence of any of the following toxicities will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

1. Any Grade 4 or greater adverse event per the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5.0) observed within 90 days of the last dose of radiation therapy.
2. Grade 3 nonhematologic toxicity (not laboratory) lasting >5 days despite optimal supportive care.
3. Any Grade 3 nonhematologic laboratory value if:
 - Medical intervention is required to treat the patient, or
 - The abnormality leads to hospitalization, or
 - The abnormality persists for >1 week.
4. Febrile neutropenia.
5. Thrombocytopenia $<25000/\text{mm}^3$ if associated with bleeding requiring intervention.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.

Management and dose modifications associated with the above adverse events are outlined in Section 7.

Dose escalation will proceed within each cohort according to the following scheme. DLT is defined above.

The following table describes the dose escalation/de-escalation rule under the BOIN design for **the starting dose level (A2; B1 in Table 1)**. Eight patients will be treated. The target DLT rate is 0.33 and the dose elimination rate is 0.75. No decision will be made regarding dosing until all eligible participants are assessed for DLT.

Number of patients treated at current dose level	8
Escalate if # of DLT $\leq$	2
De-escalate if # of DLT $\geq$	4
Eliminate if # of DLT $\geq$	4

If the number of DLTs required for dose de-escalation (4) and elimination (4) are reached after eight patients have been studied: 1) the 8 Gy x 3 SBRT dose will be eliminated; 2) a single agent BOIN design will be implemented for the three dose levels of BAY 1895344 at the 7 Gy x 3 SBRT dose level.

If two or fewer DLTs are observed in eight patients studied, then the 7 Gy x 3 SBRT dose level will be eliminated and a single agent BOIN design will be implemented for the three dose levels of BAY 1895344 at the 8 Gy x 3 SBRT dose level.

If three DLTs are observed, the A2; B1 dose will be selected as the MTD and 10 patients will be entered at this dose level in the expansion cohort.

If the 8 Gy x 3 SBRT dose is eliminated, a single-agent BOIN design will be used to determine the MTD with the target toxicity rate for the MTD of 0.33 and the dose elimination cut-off of 0.75, as above. The new starting dose will be (A1; B1) in **Table 1**. The initial cohort size is four patients, and four or eight patients will be studied at each dose level. Eight patients would be studied in the event that dose escalation occurs after treating four patients at a given dose level (*i.e.*, ≤ 1 DLT in the first four patients), but then the number of DLTs in the higher dose level results in de-escalating back down to the dose level in which four patients had already been enrolled. In the event that the DLT rate results in the (A1; B1) dose level being eliminated, the Principal Investigator will discuss with all study investigators and with CTEP whether to amend the trial to include a lower SBRT dose regimen in combination with BAY 1895344. No escalation or de-escalation of dosing will occur prior to assessment of the entire patient cohort.

The following table describes the dose escalation/de-escalation rule under the single-agent BOIN design.

# of patients treated at current dose level	4	8
Escalate if # of DLT $\leq$	1	2
De-escalate if # of DLT $\geq$	2	4
Eliminate if # of DLT $\geq$	2	4

If the number of DLTs required for dose de-escalation and elimination are reached after fewer than eight patients have been studied: 1) no additional patients will be accrued to this dose level; 2) the dose level will be eliminated.

If the 8 Gy x 3 SBRT dose is tolerated, a single-agent BOIN design will be used to determine the MTD with the target toxicity rate for the MTD of 0.33 and the dose elimination cut-off of 0.75, as above. The next dose level to be tested will be (A2; B2) in **Table 1**. The cohort size is four patients. Four or eight patients will be studied at each dose level according to the rule described for the single-agent BOIN design. No escalation or de-escalation of dosing will occur prior to assessment of the entire patient cohort.

Figure 8 describes the decision rule for the single agent design (Zhou and Yuan, 2017).

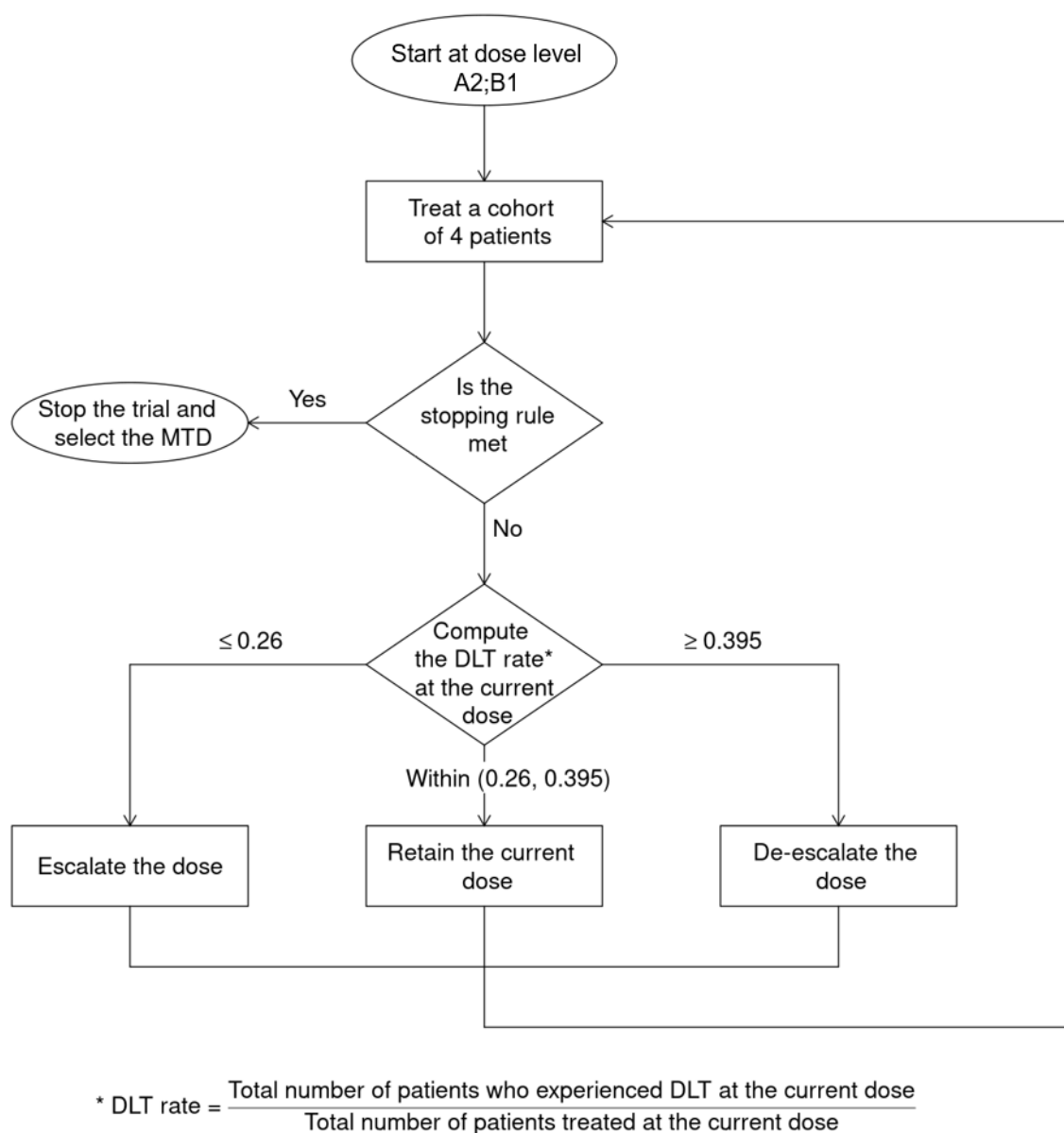


Figure 8. Flowchart of single agent BOIN design with assumptions described above.

To guide dose-escalation/de-escalation decisions under each scenario above, if the observed DLT rate at the current dose level combination is ≤ 0.26 , the next cohort of patients will be treated at the next higher dose level. However, if it is ≥ 0.395 , the next cohort will be treated at the next lower dose level. The trial design is described as follows:

1. Patients in the first cohort are treated at the starting dose combination.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Figure 8. When using Figure 8, please note the following:
 - a. “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.

- b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
 - c. If none of the actions (*i.e.*, escalation, de-escalation, or elimination) is triggered, we treat the new patients at the current dose.
 - d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
 - e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size of 24 is reached or stop the trial if the number of patients treated at the current dose reaches 8.

After the trial is completed, the MTD is selected based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the shiny app “BOIN” available at <http://www.trialdesign.org>. Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, the higher dose level is selected when the isotonic estimate is lower than the target toxicity rate; the lower dose level is selected when the isotonic estimate is greater than or equal to the target toxicity rate.

Table 2 shows the operating characteristics of the trial design based on 1,000 simulations of the trial using shiny app “BOIN” available at <http://www.trialdesign.org>. The MTD is selected with approximately 50% or greater probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.33.

Table 2. Operating characteristics of the BOIN design (Zhou and Yuan, 2017)

	1	2	3	Avg. Number of Patients	% Early Stopping
Scenario 1					
True DLT Rate	0.33	0.7	0.8		
Selection %	54.5	2.8	0		42.7
% Pts Treated	68	29.2	2.7	9.4	
Scenario 2					
True DLT Rate	0.1	0.33	0.85		
Selection %	42	51.4	0.1		6.5
% Pts Treated	41	42.8	16.2	13.9	
Scenario 3					
True DLT Rate	0.02	0.15	0.33		
Selection %	10.3	40	49.4		0.3
% Pts Treated	28.1	35.6	36.4	15.7	
Scenario 4					
True DLT Rate	0.02	0.33	0.7		
Selection %	43	54.5	2.4		0.1
% Pts Treated	38.9	42.8	18.2	14.7	
Scenario 5					

True DLT Rate	0.05	0.2	0.33	
Selection %	18.1	34.8	45.7	1.4
% Pts Treated	30.9	35	34.1	15.3

6.3 Dose Expansion Cohort

Based on simulations for dose-finding, we expect 5-8 patients to be treated at the MTD. Once the MTD is reached, an additional 10-13 patients (up to 18 total) will be treated at this dose. For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If 2 of the first 5 patients or if ≥ 2 of 6 patients experience DLT, the Principal Investigator will discuss with all study investigators and with CTEP whether additional dose levels or patients are needed to reassess the RP2D. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of BAY 1895344 or pembrolizumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. [Appendix C](#) (Patient Drug Interactions Handout and Wallet Card) should be provided to patients.

6.4.1 BAY 1895344 Concomitant Medications

Because BAY 1895344 is primarily metabolized by CYP3A4, drugs that are strong inhibitors or inducers of CYP3A4 should be avoided. BAY 1895344 has the potential to inhibit and induce CYP3A4 and 2C19, inhibit CYP2C8, 2C9, P-gp, BCRP, OAT1B1, and OAT1B3. CYP3A4 substrates with narrow therapeutic window should be avoided, and substrates of CYP2C8, 2C9, 2C19, BCRP, P-gp, OATP1B1, and OATP1B3 should be used with caution.

Because of pH-dependent solubility, antacid drugs, H2 blockers, and proton pump inhibitors may affect absorption and exposure of BAY 1895344.

6.4.2 Pembrolizumab Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with CTEP. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician; however, the decision to continue the patient on trial therapy or vaccination

schedule requires the mutual agreement of the Investigator, CTEP, and the patient.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAEs).

Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than BAY 1895344 and pembrolizumab.
- Radiation therapy other than as a treatment component of this study.
 - o Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with CTEP. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI and CTEP.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describe other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 2 cycles or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient requires systemic steroid or other immunosuppressive treatment
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
 - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
 - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.6 Duration of Follow-Up

Patients, including those removed from the study for unacceptable adverse event(s), will be followed every 13 weeks until death, withdrawal of consent, or loss to follow-up for at least 24 months. Medical record review and/or patient phone call to evaluate toxicity and vitality status is acceptable after 12 months or after confirmed disease progression, though in-person visits are preferred.

6.7 Criteria to Resume Treatment

For non-autoimmune or inflammatory events, patients may resume treatment with pembrolizumab when the drug-related AE(s) resolve to $\leq$ Grade 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin values meeting study parameters outlined in Section 7.1 should have treatment permanently discontinued.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies (not including drug-related adrenal insufficiency or hypophysitis) adequately controlled with only physiologic hormone replacement may resume treatment after replacement correction and clinically stable regimen.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the treatment should resume at the earliest convenient point that is within the 12-week delay period.

If treatment is delayed >12 weeks, the patient must be permanently discontinued from study therapy, except as specified in Section 6.5 (Duration of Therapy).

6.8 Contraception and Pregnancy

6.8.1 Contraception

Pembrolizumab and BAY 1895344 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab and BAY 1895344 have transient adverse effects on the composition of sperm.

For this trial, male patients will be considered to be of nonreproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of nonreproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR
2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR

3. Has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study treatment and for 6 months after completing BAY 1895344 therapy or 4 months after completing pembrolizumab therapy, whichever is later, by complying with one of the following:

1. Practice abstinence[†] from heterosexual activity;
OR
2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (1 of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (*e.g.*, calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 6 months after the last dose of trial therapy. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.8.2 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with BAY 1895344 and pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported without delay and within 24 hours if the outcome is a serious adverse experience (*e.g.*, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported and followed.

6.8.3 Use in Nursing Women

It is unknown whether pembrolizumab and BAY 1895344 are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment. Patients participating in this study should discontinue breast-feeding during study treatment and for 4 months after the last dose of BAY 1895344.

6.9 Discontinuation of Treatment Following Complete Response

Discontinuation of treatment may be considered for patients who have attained a confirmed complete response (CR) that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 BAY 1895344 Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events

Dose Level	BAY 1895344 Dose*
1 (starting dose)	10 mg
2	20 mg
3	30 mg
* PO for 3 doses Q12H starting before and ending after each RT fraction	

<u>Non-hematological AEs</u>	Management/Next Dose for BAY 1895344
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.

<u>Non-hematological AEs</u>	Management/Next Dose for BAY 1895344
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off the investigational agent BAY 1895344. **Patients requiring > two dose reductions should go off the investigational agent BAY 1895344.	

<u>Neutropenia</u>	Management/Next Dose for BAY 1895344
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off the investigational agent BAY 1895344. **Patients requiring > two dose reductions should go off the investigational agent BAY 1895344.	

<u>Thrombocytopenia</u>	Management/Next Dose for BAY 1895344
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off the investigational agent BAY 1895344. **Patients requiring > two dose reductions should go off the investigational agent BAY 1895344.	

7.2 Pembrolizumab Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events (revised 1-10-2023)

7.2.1 Dose Modifications

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described in Section 7.2.3.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

7.2.2 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 7.2.3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

7.2.3 Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines for irAEs and infusion reactions associated with pembrolizumab are provided in the table below.

Note that non-irAEs will be managed as appropriate, following clinical practice recommendations.

Table: Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab

General instructions: 1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone. 2. For non-endocrine-related toxicities, pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab-treatment. 3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to $\leq$ Grade 1 after a corticosteroid taper.				
irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue	Add prophylactic antibiotics for opportunistic infections	Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Patients who do not respond to corticosteroids should be seen	Monitor participants for signs and symptoms of enterocolitis (<i>i.e.</i> , diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (<i>i.e.</i> peritoneal

	Recurrent Grade 3 or Grade 4	Permanently discontinue	by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	signs and ileus) Specifically assess for celiac disease serologically, and exclude <i>Clostridium difficile</i> infection Participants with $\geq$Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 ^a	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 ^b or 4 ^c	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.
	New onset T1DM (evidence of β -cell failure) or Grade 3 or 4 hyperglycemia	Withhold ^d Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (<i>e.g.</i> anion gap, ketones, blood pH, <i>etc.</i>) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (<i>e.g.</i> GAD65, islet cell autoantibodies), and hemoglobin A1C level
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal	Monitor for signs and symptoms of hypophysitis (including

	Grade 3 or 4	Withhold or permanently discontinue ^d	replacements as clinically indicated	hypopituitarism and adrenal insufficiency) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (<i>e.g.</i> , propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue ^d		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (<i>e.g.</i> , levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

	Grade 2, 3 or 4	Permanently discontinue	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 Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event ^e		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Infusion-Related Reactions

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (<i>e.g.</i> , antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	Grade 2	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (<i>e.g.</i> from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be premedicated 1.5h ($\pm$ 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Prolonged (<i>i.e.</i> , not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (<i>e.g.</i> methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (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. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device. Note: Non-irAE will be managed as appropriate, following clinical practice recommendations. ^a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal ^b AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal ^c AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal ^d The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed. ^e Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (<i>e.g.</i> vasculitis and sclerosing cholangitis).			
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.			

Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	- Continue pembrolizumab. - 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 pembrolizumab 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 pembrolizumab.^b - If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab.^c - For facial paresis: - If event resolves fully, resume pembrolizumab.^b - If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab.^c
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	- Permanently discontinue pembrolizumab.^c - Refer patient to neurologist. - Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	- Permanently discontinue pembrolizumab.^c - 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 Pembrolizumab 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 an assessment of benefit–risk by the investigator 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 pembrolizumab can be resumed.

^c Resumption of pembrolizumab 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 pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis,	Continue pembrolizumab unless symptoms worsen or

Event	Management
Grade 1	do not improve. Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	- Permanently discontinue pembrolizumab. - 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 pembrolizumab. - Refer patient to a neurologist. - Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	- Permanently discontinue pembrolizumab. ^a - 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 ≥1 month.

^a Resumption of pembrolizumab 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 pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent

8.1.1 BAY 1895344 (NSC 810486)

Chemical Name: 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine

Classification: ATR inhibitor

CAS Registry Number: 1876467-74-1

Molecular Formula: C₂₀H₂₁N₇O

M.W.: 375 g/mol

Approximate Solubility: BAY1895344 is practically insoluble in water at pH $\geq$ 4.5, slightly soluble in ethanol, acetonitrile and acetone and sparingly soluble in 0.1 N HCl and polyethylene glycol (PEG)400.

Mode of Action: BAY1895344 is a potent, selective inhibitor of ataxia telangiectasia and Rad3-related (ATR) pathway. Activation of the ATR pathway may be critical for survival in tumors harboring defects in DNA repair or DNA damage signaling pathways.

Description: Yellow solid.

How Supplied: Bayer supplies and the Pharmaceutical Management Branch, CTEP, DCTD, NCI distributes BAY 1895344 as oral film-coated tablets. Tablets will be packaged in bottles containing 18 tablets.

- 20 mg film-coated tablets are red and round with 6 mm diameter
- 10 mg film-coated tablets are red and round with 5 mm diameter

Tablet core components include active drug substance, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol, titanium dioxide, and ferric oxide red.

Storage: Store at or below 25 °C. Do not freeze.

If a storage temperature excursion is identified, promptly return BAY 1895344 to 25 °C or below and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life stability studies are on-going. Dispense in original package or repackaging is only allowed using 45 mL plastic high density polyethylene (HDPE) white bottle sealed with PP/PP white child-resistant screw cap.

Route of Administration: Oral

Method of Administration: Swallow tablets immediately following removal from package. Take BAY 1895344 one (1) hour before or two (2) hours after a meal with approximately 240 mL of water.

Potential Drug Interactions:

No formal DDI studies have been conducted with BAY 1895344 in humans.

In vitro, BAY 1895344 is metabolized mainly by CYP3A4 and to a much lesser extent CYP1A1. BAY 1895344 is not a P-gp or BCRP substrate. Strong inhibitors and inducers of CYP3A4 should be avoided.

BAY 1895344 is a weak to moderate inhibitor of CYP3A4, 2C8, 2C9, and 2C19 *in vitro*. BAY 1895344 had no significant inhibitory effect on CYP1A2, 2A6, 2B6, 2D6, and 2E1. *In vitro*, BAY 1895344 was also shown to be an inducer of CYP3A4 and 2C19 but not 1A2. BAY 1895344 is predicted to be a moderate inducer toward sensitive CYP3A4 substrates. CYP3A4 substrates with narrow therapeutic index should be avoided, and substrates of CYP2C8, 2C9, and 2C19 should be used with caution.

BAY 1895344 was identified as an *in vitro* inhibitor of BCRP, P-gp, BSEP, OATP1B1, and OATP1B3. The risk for clinically relevant drug-drug interactions due to inhibition of BSEP is considered to be negligible but substrates of BCRP, P-gp, OATP1B1, and OATP1B3 should be used with caution.

Because of pH dependent solubility, antacid drugs, H₂-blockers, and proton pump inhibitors may affect absorption and exposure of BAY 1895344.

Patient Care Implications:

- Women of childbearing potential and their male partners should use appropriate contraceptive measures during and for 6 months after last study drug administration.
- Breast-feeding should be discontinued during treatment and for 4 months after last study drug administration.
- Based on the UV absorption properties of BAY1895344, patients should be instructed to use topical sun block and UV-blocking sunglasses during treatment with BAY1895344. Direct exposure of patients to sun light after administration should be avoided.

Availability

BAY 1895344 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

BAY 1895344 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.1.2 Agent Ordering and Agent Accountability

- 8.1.2.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one

lead participating investigator at that institution.

Sites can place orders only after enrollment onto the study. Please provide the patient ID # in the comment field when placing orders.

Submit agent requests through the PMB AURORA application. Access to AUORA requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

- 8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of a CTEP IAM account and the maintenance of an “active” account status, a “current” password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB AURORA application: <https://ctepcore.nci.nih.gov/aurora>
- CTEP Identity and Access Management (IAM) account: <https://ctepcore.nci.nih.gov/iam/>
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 **Commercial Agent**

8.2.1 Pembrolizumab (NSC 776864)

Product Description: Pembrolizumab is a commercially available humanized monoclonal IgG4

kappa antibody against the programmed death receptor-1 (PD-1) protein (KEYTRUDA[®] Package Insert, 2020). Pembrolizumab has an approximate molecular weight of 149 kDa and is produced in recombinant Chinese hamster ovary (CHO) cells.

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 of solution contains 25 mg pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Solution Preparation: Refer to the package insert for standard preparation instructions.

Route of Administration: Pembrolizumab is administered as a diluted solution (1-10 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP) intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Other drugs should not be co-administered through the same infusion line.

Agent Ordering: Pembrolizumab is commercially available.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a multi-center, single-arm, open-label phase I (dose escalation and dose expansion) study to determine the MTD for BAY 1895344 and concurrent SBRT with pembrolizumab for recurrent head and neck cancer. The primary endpoint of the dose escalation phase is to determine the MTD of BAY 1895344 and concurrent SBRT reirradiation with pembrolizumab. The dose-escalation phase will utilize a Bayesian Optimal Interval Design (BOIN) to determine the MTD for combined BAY 1895344 and SBRT.

After completion of the initial dose-finding phase, there will be an expansion cohort at the MTD in order to provide better characterization of the late toxicity profile (Section 6.3) and determine the RP2D. The primary endpoint of the dose expansion phase will be late toxicities within 1 year of treatment initiation. Up to 18 patients will be studied for safety at the MTD, including those entered on the dose-finding portion of this study (minimum 4; maximum 8 patients). The proportions of total patients experiencing late toxic events will be estimated at 6 months, 1 year, and 2 years post SBRT. The RP2D will be reassessed once late toxicity data are available for the expansion cohort at 1 year post-treatment before proceeding to a phase 2 clinical trial. If at any time the late toxicity rate at 1 year is ≥ 0.33 (1 of 1; ≥ 1 of 2; ≥ 1 of 3; ≥ 2 of 4, 5, 6; ≥ 3 of 7, 8, 9; ≥ 4 of 10, 11, 12; ≥ 5 of 13, 14, 15; ≥ 6 of 16, 17, 18), then the study team will determine if the study should be suspended to investigate and consider dose reduction.

We anticipate that approximately a third of patients (n=6) will die of disease within the first year post-treatment. A competing risk analysis for survival and time to DLT will be conducted, and

the cumulative incidence and 95% confidence interval of DLT will be estimated. If the observed cumulative incidence of DLT is greater than 0.33, the Principal Investigator will discuss with CTEP and all study investigators to determine whether additional patients are needed to re-assess the MTD. (If the true DLT rate is 0.33, the probability of observing 6 or more DLTs in 12 patients is 0.17.) If there are high rates of late toxicity in the dose level selected, then a second dose-expansion cohort could be enrolled with a lower dose level that did not result in high rates of late toxicity.

9.2 Sample Size/Accrual Rate

Total anticipated accrual is 37 patients, with the total number depending on the number of dose levels necessary to determine the MTD. We anticipate an accrual of 1 patient/month. There will be periods of time when accrual will be held while patients enrolled on the current dose cohort are observed for DLTs.

PLANNED ENROLLMENT REPORT

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	1	5	0	1	7
White	6	19	0	2	27
More Than One Race	0	1	0	0	1
Total	7	27	0	3	37

PHS 398 / PHS 2590 (Rev. 03/20 Approved Through 2/28/2023)

OMB No. 0925-0001/0002

9.3 Stratification Factors

There will be no stratification factors. However, there will be a pre-planned subgroup analysis to compare outcomes for patients with immuno-oncology-naïve disease *versus* patients with a history of progression on immuno-oncology. Additionally, there will be a pre-planned subgroup analysis to compare outcomes for patients with human papillomavirus (HPV)-related disease *versus* HPV-negative disease.

9.4 Analysis of Secondary Endpoints

9.4.1 12-month toxicity (quantification of number of toxicities and toxicity grade)

The frequency and percentage of adverse events (AEs) will be provided overall and by dose level for any grade and attribution as well as for Grade 3 or greater AEs, at least possibly related to treatment.

9.4.2 Locoregional control

A competing risk analysis will be conducted with local failure, distal failure, and death as competing events. The cumulative incidence and 95% confidence interval for local failure will be estimated. Time to each event will be measured from the start of treatment regimen (D1 pembrolizumab).

9.4.3 Progression-free survival

Progression-free survival (PFS) will be measured from the start of treatment regimen (D1 pembrolizumab) until documented local or distal failure or death from any cause. PFS will be estimated using the method of Kaplan-Meier.

9.4.4 Overall response rate

Overall response will be defined as a CR or PR based on the RECIST 1.1 criteria. The proportion of patients responding to the treatment regimen and corresponding 95% confidence interval estimates will be calculated.

9.4.5 1-year overall survival

Overall survival (OS) will be measured from the start of treatment regimen (D1 pembrolizumab) until death from any cause. The Kaplan-Meier method will be used to estimate 1-year OS.

9.4.6 Quality of life (H&N-specific questionnaire) at 3, 6, and 12 months

The frequency and percentage of responses to the quality of life (QOL) questionnaire will be summarized at 3, 6, and 12 months post-treatment and interpreted descriptively.

9.5 Analysis of Exploratory Endpoints

Associations between potential predictive biomarkers of response to BAY 1895344, SBRT, and pembrolizumab (including but not limited to baseline tumor *ATM* mutation status, tumor mutation burden, baseline circulating tumor DNA level, tumor PD-L1 expression, HPV status, and change in circulating Ki67⁺ CD8⁺ T-cells relative to baseline) will be investigated. Tumor mutation burden will be categorized as High (above median) or Low (equal to or below median). Other biomarker expression levels will be categorized as High versus Absent/Reduced. The Chi-square or Fisher exact test will be used to study associations between expression levels and tumor response (CR/PR; Stable/PD). For example, we hypothesize that patients with mutant *ATM* (including point mutations, insertions, deletions, copy number variations, and loss of heterozygosity) will exhibit improved response to ATR inhibition with BAY 1895344 compared to patients with intact *ATM*. Similarly, we hypothesize that patients with PD-L1⁺ tumors will have better overall response rate and OS than patients with PD-L1⁻ tumors. Similarly, we hypothesize that patients with high tumor mutation burden will have better overall response rate and OS than patients with low tumor mutation burden. Associations with time-to-event endpoints will be investigated using the log rank test. Differences in change in circulating Ki67⁺ CD8⁺ T-cells relative to baseline between levels of tumor response will be explored using the t-test or non-parametric equivalent (*e.g.*, Mann-Whitney) if appropriate. Cox regression will be used to explore associations between change in circulating Ki67⁺ CD8⁺ T-cells and time-to-event endpoints. Other biomarkers will be analyzed similarly. A significance level of 0.1 will be used in these analyses and no adjustment will be made for multiple comparisons.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

10.1.1 CAEPR for CTEP IND Agent

10.1.1.1 CAEPR for BAY 1895344 (NSC 810486)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ae guidelines.pdf for further clarification. *Frequency is provided based on 197 patients.* Below is the CAEPR for BAY 1895344.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, September 5, 2020¹

Adverse Events with Possible Relationship to BAY 1895344 (CTCAE 5.0 Term) [n= 197]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			<i>Anemia (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
	Diarrhea		
Nausea			<i>Nausea (Gr 2)</i>
	Vomiting		<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			<i>Fatigue (Gr 2)</i>
INVESTIGATIONS			
Neutrophil count decreased			<i>Neutrophil count decreased (Gr 2)</i>
Platelet count decreased			<i>Platelet count decreased (Gr 2)</i>
White blood cell decreased			<i>White blood cell decreased (Gr 2)</i>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on BAY 1895344 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BAY 1895344 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

GASTROINTESTINAL DISORDERS - Abdominal pain; Dysphagia

INFECTIONS AND INFESTATIONS - Shingles

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (medication error)

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased

METABOLISM AND NUTRITION DISORDERS - Hypokalemia; Hypophosphatemia

NERVOUS SYSTEM DISORDERS - Dysgeusia; Presyncope

PSYCHIATRIC DISORDERS - Irritability

RENAL AND URINARY DISORDERS - Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular

VASCULAR DISORDERS - Hypotension

Note: BAY 1895344 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.2 CAEPR for Commercial Agent

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pembrolizumab (MK-3475, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ae guidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for Pembrolizumab (MK-3475).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, December 13, 2022¹

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia ²		
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura) ²	
	Lymph node pain ²		
CARDIAC DISORDERS			
		Myocarditis ²	
		Pericarditis ²	
ENDOCRINE DISORDERS			
	Adrenal insufficiency ²		
		Endocrine disorders - Other (hypoparathyroidism)	
	Endocrine disorders - Other (thyroiditis) ²		
	Hyperthyroidism ²		
	Hypophysitis ²		
	Hypopituitarism ²		
	Hypothyroidism ²		
EYE DISORDERS			
		Uveitis ²	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis ²		
	Diarrhea ²		Diarrhea ² (Gr 2)
	Mucositis oral ²		
	Nausea		Nausea (Gr 2)
	Pancreatitis ²		
	Small intestinal mucositis ²		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills ²		
Fatigue			Fatigue (Gr 2)
	Fever ²		
HEPATOBIILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis) ²		
		Hepatobiliary disorders - Other (sclerosing cholangitis)	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis ²	
		Cytokine release syndrome ²	
		Immune system disorders - Other (acute graft-versus-host-disease) ^{2,3}	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis) ²	
	Immune system disorders - Other (sarcoidosis) ²		
		Serum sickness ²	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased ²		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased ²		
	Blood bilirubin increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis) ²	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus) ²	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia ²		Arthralgia ² (Gr 2)
	Arthritis ²		
	Back pain		
	Joint range of motion decreased		
	Myalgia ²		
	Myositis ²		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome ²	
		Nervous system disorders - Other (myasthenic syndrome) ²	
		Nervous system disorders - Other (neuromyopathy) ²	
		Nervous system disorders - Other (non-infectious encephalitis) ²	
		Nervous system disorders - Other (non-infectious meningitis) ²	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (optic neuritis)	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Nervous system disorders - Other (polyneuropathy) ²	
		Paresthesia	
		Peripheral motor neuropathy ²	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis) ²	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pneumonitis ²		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis ²		
		Erythema multiforme ²	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus ²		Pruritus ² (Gr 2)
	Rash acneiform ²		
	Rash maculo-papular ²		Rash maculo-papular ² (Gr 2)
	Skin and subcutaneous tissue disorders - Other (dermatitis) ²		
	Skin hypopigmentation ²		
		Stevens-Johnson syndrome ²	
		Toxic epidermal necrolysis	
	Urticaria ²		
VASCULAR DISORDERS			
		Vasculitis ²	

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

³Acute graft-versus-host disease has been observed in patients treated with Pembrolizumab (MK-3475) who received hematopoietic stem cell transplants.

Adverse events reported on Pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other

(pancytopenia); Disseminated intravascular coagulation; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia

EYE DISORDERS - Eye pain

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain

INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion²; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity

NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain²; Pneumothorax; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
 - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.
- **Attribution** of the AE:
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened condition should be reported as a routine AE.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctscontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents > Protocol Related Documents > Adverse Event Reporting*, and
- Additional resources: *Resources > CTSU Operations Information > User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 “Disease progression”** in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1, 2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) NOTE: Investigators <u>MUST</u> immediately report to the sponsor (NCI) <u>ANY</u> SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). An AE is considered serious if it results in <u>ANY</u> of the following outcomes: 1) Death 2) A life-threatening AE 3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).	
<u>ALL SAEs</u> that meet the above criteria <u>MUST</u> be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.	
Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days
NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. <u>Expedited AE reporting timeframes are defined as:</u> ○ “24-Hour notification, 5 Calendar Days” - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. ○ “24-Hour notification, 10 Calendar Days” - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.	
¹SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-Hour notifications are required for all SAEs followed by a complete report • Within 5 calendar days for Grade 3-5 SAEs • Within 10 calendar days for Grade 1-2 SAEs ²For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.	

Effective Date: August 30, 2024

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS unless they result in ≥ 24 h hospitalization of a patient. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE v5.0 SOC	Adverse Event	Grade	Resulting in Hospitalization ≥ 24 hrs
Gastrointestinal disorders	Mucositis oral	2	No
Gastrointestinal disorders	Oral pain	2	No
Injury, poisoning and procedural complications	Dermatitis radiation	2	No

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

With the exception of imaging, baseline evaluations are to be conducted within 21 days prior to start of protocol therapy. Baseline imaging must be done ≤ 6 weeks prior to the start of therapy (preferably ≤ 4 weeks). Baseline imaging must include neck CT (preferably contrast-enhanced) and either non-contrast chest CT or skullbase to mid-thigh PET/CT (preferably with contrast-enhanced neck CT if another diagnostic contrast-enhanced neck CT is not available). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

		On Treatment						Post Radiation Therapy Period ⁱ							Off Study due to toxicity during C1 or C2 ^a	Off Study due to progression ^a
	Pre-Study	Cycle 1			Cycle 2			2 Weeks Post-RT (±1 wk)	4 Weeks Post-RT (± 1 wk)	13 Weeks Post-RT (± 2 wk)	26 Weeks Post-RT (±2 wk)	39 Weeks Post-RT (± 3 wk)	1 Year Post-RT (± 6 wk)	Long-Term Post-RT ^j		
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3									
BAY 1895344		A	A	A	A	A										
Pembrolizumab		B			B											
Radiation therapy (SBRT)					C	C										
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X	X-----X (including continued anti-PD-1 therapy or any other cancer therapeutics initiated after Cycle 2 pembrolizumab)													X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	if in person	X	X
Vital signs	X	X			X			X	X	X	X	X	X	if in person	X	X
Height	X															
Weight	X	X			X			X	X	X	X	X	X	if in person	X	X
Performance status ^b	X	X			X			X	X	X	X	X	X	X	X	X
Dental evaluation ^c	X															
CBC w/diff, plts	X	X	X	X	X	X	X								X	
Comprehensive chemistry panel ^d	X	X	X	X	X	X	X								X	
Coags (PT/INR,	X															

		On Treatment						Post Radiation Therapy Period ⁱ							Off Study due to toxicity during C1 or C2 ^a	Off Study due to progression ^a
	Pre-Study	Cycle 1			Cycle 2			2 Weeks Post-RT (± 1 wk)	4 Weeks Post-RT (± 1 wk)	13 Weeks Post-RT (± 2 wk)	26 Weeks Post-RT (± 2 wk)	39 Weeks Post-RT (± 3 wk)	1 Year Post-RT (± 6 wk)	Long-Term Post-RT ^j		
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3									
aPTT)																
Thyroid profile	X ^f						X ^f									
EKG (as indicated)	X															
Adverse event evaluation			X-----X												X ^g	X ^g
Tumor measurements	X		Tumor measurements (by physical exam for visible/palpable tumors) are repeated every 13 weeks. If persistent or new disease is detectable on imaging at 13 weeks post-RT, then radiologic evaluation should be repeated at least every 13 weeks for RECIST evaluation.													X
Radiologic evaluation	X									X	As indicated	As indicated	As indicated	As indicated		As indicated
Pregnancy test ^c	X	X			X											
Archival Tumor Tissue Collection	X															
Blood collection for plasma and PBMCs	X		X			X					X		X			X ^h
Blood collection (Streck cfDNA)	X															X ^h
Quality of Life assessment	X									X	X		X			
In clinic visit (preferred), medical record review, and/or phone call to evaluate patient status														X ^j		
A: BAY 1895344: Cycle 1: 30 mg during Cycle 1, PO Q12H starting Day 7 for 3 days on/4 days off for 2 weeks. Dose as assigned during dose escalation Cycle 2, PO Q12H for 3 doses surrounding each SBRT fraction with first (morning) dose at least 1 hour before each fraction of SBRT and no more than 6 hours before each fraction of SBRT (i.e., 9 doses total). MTD during dose expansion Cycle 2, PO Q12H for 3 doses surrounding each SBRT fraction B: Pembrolizumab: 200 mg IV, Day 1 of each cycle; It is recommended that pembrolizumab continue after the first two cycles, but continuation of pembrolizumab is at the discretion of the treating medical oncologist. The number of additional cycles of pembrolizumab after the two cycles on study will be recorded. C: SBRT: Dose as assigned, starting between Days 2 and 8 of Cycle 2, with at least 2 days without radiation between fractions, no more than 3 days without radiation between fractions, and no more than 2 fractions per week (e.g. Monday/Thursday/Monday). a: Off-study evaluation. Patients are considered to be “off-study due to toxicity” if they are removed from the study for unacceptable adverse event(s) before completing both cycles of study treatment. These patients are evaluable for toxicity, but not for treatment response. Patients are considered to be “off-study due to progression” if they develop progressive or																

		On Treatment						Post Radiation Therapy Period ⁱ							Off Study due to toxicity during C1 or C2 ^a	Off Study due to progression ^a	
	Pre-Study	Cycle 1			Cycle 2			2 Weeks Post-RT (±1 wk)	4 Weeks Post-RT (± 1 wk)	13 Weeks Post-RT (± 2 wk)	26 Weeks Post-RT (±2 wk)	39 Weeks Post-RT (± 3 wk)	1 Year Post-RT (± 6 wk)	Long-Term Post-RT ^j			
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3										
		recurrent disease. Any patient who received radiation therapy should continue to be followed for quarterly (every 13 weeks) radiation toxicity/safety assessments for at least one year after completing SBRT, and if feasible until death, withdrawal of consent, or loss to follow-up. While in-person follow-up is preferred, this assessment can be performed via telephone and/or medical record review.															
b:	Note: Performance status evaluations are based on a 3 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.																
c:	Recommended for non-edentulous patients prior to beginning study treatment.																
d:	Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.																
e:	Pregnancy test for women of childbearing potential.																
f:	Thyroid testing (should include free T4, TSH) after completion of Cycle 2. This should be performed either before or at the 2 week post-RT visit.																
g:	Patients, including those removed from the study for unacceptable adverse event(s), will be followed for quarterly (every 13 weeks) radiation toxicity/safety assessments for at least one year after the Off-study visit, but ideally until death, withdrawal of consent, or loss to follow-up. It is recommended that these assessments be in person, but it is acceptable for these assessments to occur via phone.																
h:	Optional blood collection at disease progression.																
i:	Patients will be evaluated per the Post Radiation Therapy Period schedule by a radiation oncologist with physical exam (including fiberoptic laryngoscopy), vital signs, performance status, and adverse event evaluation for one year after completing radiation therapy. Assessment should include radiologic evaluation if persistent/new disease was noted at the last visit or if history/physical exam findings are concerning for residual/progressive disease. In the second year after completing radiation therapy (Long-Term Post-RT), patients will ideally continue to be evaluated in person every 13 weeks (+/- 6 weeks). If any of these follow-up evaluations are performed by a provider not at the clinical trial site, clinic notes should be securely sent to the clinical trial team for data extraction. Each visit is calculated from the date of the patient's final radiation therapy treatment.																
j:	Patients will be followed every 13 weeks (+/- 6 weeks) for at least one year after their Off Study or 1 Year Post-RT visit. This can be done by in-clinic visits, phone call, and/or medical record review to evaluate patient status.																

12. MEASUREMENT OF EFFECT

Although the clinical benefit of the combination of BAY 1895344, pembrolizumab, and SBRT has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated in radiation oncology clinic at least every 13 weeks with history and physical exam for at least one year post-RT. When feasible, follow-up every 13 weeks should be continued for two years post-RT. In addition to a baseline scan, a repeat scan (contrast-enhanced neck CT and non-contrast chest CT or contrast-enhanced neck CT and skullbase to mid-thigh PET/CT) will also be obtained 13 weeks (± 2 weeks) following completion of radiation therapy for initial documentation of response. Follow-up visits after the 13-week post-RT evaluation should include radiologic evaluation if persistent/new disease was noted at the prior visit or if history/physical exam findings are concerning for residual/progressive disease. While it is strongly preferred that follow-up evaluations will be performed by a provider at the clinical trial site, follow-up visits in the second year after RT can be performed at other locations with clinic notes sent securely to the clinical trial team for data extraction.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response by physical exam (including fiberoptic laryngoscopy, if this procedure is necessary to visualize gross tumor) at 2 and 4 weeks following completion of RT. Physical exam and post-treatment scan (contrast-enhanced neck CT or skullbase to mid-thigh PET/CT with contrast-enhanced neck CT) will be performed at 13 weeks (± 2 weeks) following completion of RT (first scan after pre-treatment, baseline imaging). If metastatic disease is present at baseline, the post-treatment scan should also include the site(s) of distant disease. For example, if lung metastases were present on the baseline exam, then chest CT should be performed at 13 weeks following completion of RT. If initial post-treatment imaging results are equivocal or residual disease is observed, then repeat imaging will be performed 8-14 weeks later. Any subsequent imaging after a documented complete response will be performed at the discretion of the treating physician. Continued surveillance imaging every 13 weeks after treatment completion is recommended but not required. However, repeat imaging should be performed for any signs, symptoms or physical exam findings concerning for recurrent disease.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with BAY 1895344.

Evaluable for Objective Response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (≥ 2 cm) by chest x-ray or as ≥ 10 mm (≥ 1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm (≥ 1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] or pathological lymph nodes with ≥ 10 to < 15 mm [≥ 1 to < 1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target Lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions

with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm (≥ 1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

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

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

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

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

12.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the

treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. <u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.				

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5 Duration of Response

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

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

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

12.1.6 Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.1.7 Response Review

For trials where the response rate is the primary endpoint, it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, the Protocol Principal Investigator

will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and
- Assigned a Rave role on the relevant LPO or PO roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
Rave role requirements:
 - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
 - Rave Investigator role, must be registered as a Non-Physician Investigator (NPPIVR) or Investigator (IVR), and
 - Rave Read Only role, or RAVE SLA role must have at minimum an Associates (A) registration type.

Refer to <https://ctep.cancer.gov/investigatorResources/default.htm> for registration types and documentation required.

If the study has a Delegation of Task Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings

(eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctscontact@westat.com.

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPiVR), or Investigator (iVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at <https://triadinstall.acr.org/triadclient/>.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at <http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11>. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (<http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models>). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly

basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

13.4 CTEP Multicenter Guidelines

UPMC Hillman Cancer Center is the "Coordinating Center" liaising with CTEP as the lead site on amendments, approvals and facilitating broadcasting protocol updates on CTSU website. UPMC Hillman Cancer Center will also conduct monthly site calls to update all sites on protocol and patient updates tracking accruals, safety etc. for all sites. The clinical trial team can be

reached at ETCTN10405@upmc.edu for additional information.

13.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
 - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of

human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

14. REFERENCES

- American Cancer Society. (2018). Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018.
- Bannik, K., S. Zitzmann-Kolbe, A. Scholz, *et al.* (2019). Radium-223 α -particle radiation: Characterization of the *in vitro* effects on cancer cells in monotherapy and in combination with DNA repair inhibitors. *Cancer Res (AACR Annual Meeting)*. 79:3927 (abstract).
- Chaturvedi, A.K., E.A. Engels, R.M. Pfeiffer, *et al.* (2011). Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 29:4294-4301.
- Chemnitz, J.M., R.V. Parry, K.E. Nichols, *et al.* (2004). SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T-cell stimulation, but only receptor ligation prevents T-cell activation. *J Immunol.* 173:945-954.
- Chinn, S.B., and J.N. Myers. (2015). Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions. *J Clin Oncol.* 33:3269-3276.
- Cimprich, K.A., and D. Cortez. (2008). ATR: an essential regulator of genome integrity. *Nat Rev Mol Cell Biol.* 9:616-627.
- De Bono, J.S., D.S.P. Tan, R. Caldwell, *et al.* (2019). First-in-human trial of the oral ataxia telangiectasia and Rad3-related (ATR) inhibitor BAY 1895344 in patients (pts) with advanced solid tumors. *J Clin Oncol.* 37:3007
- Dillon, M.T., H.E. Barker, M. Pederson, *et al.* (2017). Radiosensitization by the ATR Inhibitor AZD6738 through Generation of Acentric Micronuclei. *Mol Cancer Ther.* 16:25-34.
- Dillon, M.T., K.F. Bergerhoff, M. Pederson, *et al.* (2019). ATR Inhibition Potentiates the Radiation-induced Inflammatory Tumor Microenvironment. *Clin Cancer Res.* 25:3392-3403.
- Disis, M.L. (2010). Immune Regulation of Cancer. *J Clin Oncol.* 28:4531-4538.
- Dudley, M.E., J.R. Wunderlich, J.C. Yang, *et al.* (2005). Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol.* 23:2346–2357.
- Eisenhauer, E.A., P. Therasse, J. Bogaerts, *et al.* (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). *Eur J Cancer.* 45:228-47.
- Fitzmaurice, C., C. Allen, R.M. Barber, *et al.* (2017). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability-Adjusted Life-years for 32 Cancer Groups, 1990-2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 3:524-548.

Fokas, E., R. Prevo, E.M. Hammond, *et al.* (2014). Targeting ATR in DNA damage response and cancer therapeutics. *Cancer Treat Rev.* 40:109-117.

Francisco, L.M., P. Sage, A.H. Sharpe. (2010). The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev.* 236:219-242.

Fujisawa, H., N.I. Nakajima, S. Sunada, *et al.* (2015). VE-821, an ATR inhibitor, causes radiosensitization in human tumor cells irradiated with high LET radiation. *Radiat Oncol.* 10:175.

Gaudio, E., C. Tarantelli, F. Spriano, *et al.* (2019). The ATR inhibitor BAY 1895344 shows strong preclinical activity in lymphomas and appears associated with specific gene expression signatures. *Cancer Res (AACR Annual Meeting).* 79:274 (abstract).

Greenwald, R.J., G.J. Freeman, A.H. Sharpe. (2005). The B7 family revisited. *Annu Rev Immunol.* 23:515-548.

Huang, S.H., W. Xu, J. Waldron, *et al.* (2015). Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas. *J Clin Oncol.* 33:836-845.

Huang, A.C., R.J. Orlowski, X. Xu, *et al.* (2019). A Single Dose of Neoadjuvant PD-1 Blockade Predicts Clinical Outcomes in Resectable Melanoma. *Nat Med.* 25:454-461.

Hunder, N.N., H. Wallen, J. Cao, *et al.* (2008). Treatment of metastatic melanoma with autologous CD4+ T-cells against NY-ESO-1. *N Engl J Med.* 358:2698-2703.

Investigator's Brochure. (2020). BAY 1895344. Bayer AG. Version 6.0. August 6, 2020.

Investigator's Brochure. (2020). MK-3475. Edition Number 19. Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc. September 4, 2020.

Kamphorst, A.O., R.N. Pillai, S. Yang, *et al.* (2017). Proliferation of PD-1⁺ T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients. *Proc Natl Acad Sci U S A.* 114:4993-4998.

KEYTRUDA® (pembrolizumab) Package Insert. Merck & Co., Inc. Whitehouse Station, NJ. June 2020.

Kim, J.Y., A. Kronbichler, M. Eisenhut, *et al.* (2019). Tumor Mutational Burden and Efficacy of Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *Cancers (Basel).* 11:1798

Le, D.T., J.N. Uram, H. Wang, *et al.* (2015). PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med.* 372:2509-2520.

Liu, S., and Y. Yuan. (2015). Bayesian optimal interval designs for phase I clinical trials. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*. 64:507-523.

Luecking, U.T., J. Lefranc, A. Wengner, *et al.* (2017). Identification of potent, highly selective and orally available ATR inhibitor BAY 1895344 with favorable PK properties and promising efficacy in monotherapy and combination in preclinical tumor models. *Cancer Res (AACR Annual Meeting)*. 77:983 (abstract).

Menezes, D.L., J. Holt, Y. Tang, *et al.* (2015). A synthetic lethal screen reveals enhanced sensitivity to ATR inhibitor treatment in mantle cell lymphoma with ATM loss-of-function. *Mol Cancer Res*. 13:120-129.

O'Sullivan, B., S.H. Huang, J. Su, *et al.* (2016). Development and Validation of a Staging System for HPV-related Oropharyngeal Cancer by the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S): A Multicentre Cohort Study. *Lancet Oncol*. 17:440-451.

Okazaki, T., A. Maeda, H. Nishimura, *et al.* (2001). PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domaincontaining tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci USA*. 98:13866-13871.

Oliva, M., A. Sreafico, M. Taberna, *et al.* (2019). Immune biomarkers of response to immune-checkpoint inhibitors in head and neck squamous cell carcinoma. *Ann Oncol*. 30:57-67.

Parry, R.V., J.M. Chemnitz, K.A. Frauwirth, *et al.* (2005). CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol*. 25:9543-9553.

Pitts, T.M., S.L. Davis, S.G. Eckhardt, and E.L. Bradshaw-Pierce. (2014). Targeting nuclear kinases in cancer: development of cell cycle kinase inhibitors. *Pharmacol Ther*. 142:258-269.

Reaper, P.M., M.R. Griffiths, J.M. Long, *et al.* (2011). Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. *Nat Chem Biol*. 7:428-430.

Riley, J.L. (2009). PD-1 signaling in primary T-cells. *Immunol Rev*. 229:114-125.

Rizvi, N.A., M.D. Hellmann, A. Snyder, *et al.* (2015). Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 348:124-128.

Sankunny, M., R.A. Parikh, D.W. Lewis, *et al.* (2014). Targeted inhibition of ATR or CHEK1 reverses radioresistance in oral squamous cell carcinoma cells with distal chromosome arm 11q loss. *Genes Chromosomes Cancer*. 53:129-143.

Sheppard, K.A., L.J. Fitz, J.M. Lee, *et al.* (2004). PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett*. 574:37-41.

Snyder, A., V. Makarov, T. Merghoub, *et al.* (2014). Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med.* 371:2189-2199.

Truong, M.T., R.N. Nadgir, A.E. Hirsch, *et al.* (2010). Brachial Plexus Contouring with CT and MR Imaging in Radiation Therapy Planning for Head and Neck Cancer. *Radiographics.* 30:1095-1103.

Tu, X., M.M. Kahila, Q. Zhou, *et al.* (2018). ATR Inhibition is a Promising Radiosensitizing Strategy for Triple-Negative Breast Cancer. *Mol Cancer Ther.* 17:2462-2472.

Union for International Cancer Control. (2014). Head and Neck Cancer. Review of Cancer Medicines on the WHO List of Essential Medicines.

Vargo, J.A., R.L. Ferris, J. Ohr, *et al.* (2015). A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 91:480-488.

Vendetti, F.P., P. Karukonda, D.A. Clump, *et al.* (2018). ATR Kinase Inhibitor AZD6738 Potentiates CD8⁺ T Cell-Dependent Antitumor Activity Following Radiation. *J Clin Invest.* 128:3926-3940.

Weber, A.M., and A.J. Ryan. (2015). ATM and ATR as therapeutic targets in cancer. *Pharmacol Ther.* 149:124-138.

Wen, Y. and J.R. Grandis. (2015). Emerging drugs for head and neck cancer. *Expert Opin Emerg Drugs.* 20:313-329.

Wengner, A.M., G. Siemeister, U. Luecking, *et al.* (2018). Synergistic *in vivo* activity of the ATR inhibitor BAY 1895344 in combination with the targeted alpha therapy radium-223 dichloride in a preclinical tumor model mimicking bone metastatic castration-resistant prostate cancer (mCRPC). *Cancer Res (AACR Annual Meeting).* 78:838 (abstract).

Wengner, A.M., D. Kirchhoff, L. Roese, *et al.* (2019). Synergistic activity of the ATR inhibitor BAY1895344 in combination with immune checkpoint inhibitors in preclinical tumor models. *Cancer Res.* 79:Abstract 272.

Wengner, A.M., G. Siemeister, U. Luecking, *et al.* (2020). The novel ATR inhibitor BAY 1895344 is efficacious as monotherapy and combined with DNA damage-inducing or repair-compromising therapies in preclinical cancer models. *Mol Cancer Ther.* 19:26-38.

Wickstroem, K., U.B. Hagemann, V. Cruciani, *et al.* (2019a). Synergistic effect of a mesothelin targeted thorium-227 conjugate in combination with DNA damage response inhibitors in ovarian cancer xenograft models. *J Nucl Med.* 60:1293-1300.

Wickstroem, K., U.B. Hagemann, A. Kristian, *et al.* (2019b). Preclinical combination studies of an FGFR2 targeted thorium-227 conjugate and the ATR inhibitor BAY 1895344. *Int J Radiat Oncol Biol Phys.* 105:410-422.

Yan, S., M. Sorrell, and Z. Berman. (2014). Functional interplay between ATM/ATR-mediated DNA damage response and DNA repair pathways in oxidative stress. *Cell Mol Life Sci.* 71:3951-3967.

Zeman, M.K., and K.A. Cimprich. (2014). Causes and consequences of replication stress. *Nat Cell Biol.* 16:2-9.

Zhang, X., J.C. Schwartz, X. Guo, *et al.* (2004). Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity.* 20:337-347.

Zhou, Y., and Y. Yuan. (2017). Bayesian Optimal Interval Designs for Phase I Clinical Trials: Version 1.0.0, Web, available at <http://www.trialdesign.org>.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease 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 B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. <u>Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey <i>et al.</i>, 2009).</u>		
Formulae:		
Race and Sex	Serum Creatinine (SCr), $\mu\text{mol/L}$ (mg/dL)	Equation
Black	Female ≤ 62 (≤ 0.7)	$\text{GFR} = 166 \times (\text{SCr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	Female > 62 (> 0.7)	$\text{GFR} = 166 \times (\text{SCr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
	Male ≤ 80 (≤ 0.9)	$\text{GFR} = 163 \times (\text{SCr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	Male > 80 (> 0.9)	$\text{GFR} = 163 \times (\text{SCr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
White or other	Female ≤ 62 (≤ 0.7)	$\text{GFR} = 144 \times (\text{SCr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	Female > 62 (> 0.7)	$\text{GFR} = 144 \times (\text{SCr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
	Male ≤ 80 (≤ 0.9)	$\text{GFR} = 141 \times (\text{SCr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	Male > 80 (> 0.9)	$\text{GFR} = 141 \times (\text{SCr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
SCr in mg/dL; Output is in mL/min/1.73 m ² and needs no further conversions.		
2. <u>eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey <i>et al.</i>, 2006).</u>		
$175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black)		
Output is in mL/min/1.73 m ² and needs no further conversions.		
3. <u>Estimated creatinine clearance (CLCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).</u>		
$\text{CLCr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \{ \times 0.85 \text{ for female patients} \}$		
Followed by conversion to a value normalized to 1.73 m ² with the patient's body surface area (BSA).		

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al.* (2009). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al.* (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 145:247-254.
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron.* 16:31-41.

APPENDIX C PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

<u>Patient Name:</u>	<u>Diagnosis:</u>	<u>Trial #:</u> 10405
<u>Study Doctor:</u>	<u>Study Doctor Phone #:</u>	<u>Study Drugs:</u> BAY 1895344 Pembrolizumab

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

BAY 1895344 interacts with certain specific enzyme(s) in your liver or other tissues like the gut, and certain transport proteins that help move drugs in and out of cell.

	Explanation
CYP isoenzymes	The enzymes in question are CYP3A4, 2C8, 2C9, and 2C19 . BAY 1895344 is broken down by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. Strong inhibitors and inducers of CYP3A4 should be avoided. BAY 1895344 weakly to moderately inhibits CYP3A4, CYP2C8 2C9, and 2C19. BAY 1895344 induces CYP3A4 and 2C19. Substrates of CYP3A4 with narrow therapeutic window should be avoided. Other drugs that are broken down by CYP2C8, 2C9, and 2C19 may be affected when used at the same time.
Transport proteins	The proteins in question are P-gp, BCRP, OATP1B1, and OATP1B3 . BAY 1895344 inhibits these transport proteins and may affect other drugs that require them to move in and out of the cells.

These are the things that you need to know:

The study drug BAY 1895344 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors and inducers of CYP3A4, substrates of CYP3A4 with narrow therapeutic window, substrates of CYP2C8, 2C9, 2C19, BCRP, P-gp, OATP1B1, and OATP1B3.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may

contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Make sure your doctor knows to avoid certain prescription medications.
- No grapefruit juice, Seville oranges, or grapefruit can be consumed while on BAY 1895344.
- Antacids, H2 receptor antagonists, and proton pump inhibitors should be used with caution.
- Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version Nov/2019

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE EMERGENCY INFORMATION		NIH NATIONAL CANCER INSTITUTE DRUG INTERACTIONS	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.		Carry this card with you at all times BAY 1895344 interacts with specific liver enzymes called CYP3A4, 2C8, 2C9, and 2C19 and transport proteins BCRP, P-gp, OATP1B1, and OATP1B3 and must be used very carefully with other medicines that interact with these enzymes or transporters.	
Patient Name: Diagnosis: Study Doctor: Study Doctor Phone #: NCI Trial #: 10405 Study Drugs: BAY 1895344 Pembrolizumab		Use caution and avoid the following: • No grapefruit juice, Seville oranges, or grapefruit can be consumed while on BAY 1895344. • Antacids, H2 receptor antagonists, and proton pump inhibitors should be used with caution. • Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when in the sun. Your healthcare providers should be aware of any medicines that are strong inhibitors or inducers of CYP3A4 and substrates of CYP3A4 with narrow therapeutic window, which should be avoided. Use caution with substrates of CYP2C8, 2C9, 2C19, BCRP, P-gp, OATP1B1, and OATP1B3. Before prescribing new medicines, your health care provider should check a frequently-updated medical reference for a list of drugs to avoid or contact your study doctor.	
For more information: 1-800-4-CANCER cancer.gov clinicaltrials.gov		For more information: 1-800-4-CANCER cancer.gov clinicaltrials.gov	

Version Nov/2019

APPENDIX D PATIENT MEDICATION DIARY

PATIENT'S MEDICATION DIARY – CYCLE 1

Today's date _____ Agent _____ BAY 1895344 _____

Patient Name _____ (initials acceptable)

Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take BAY 1895344 tablets twice each day, 12 hours apart, one (1) hour before or two (2) hours after a meal with approximately 240 mL (approximately 8 ounces) of water. Do not consume grapefruit juice, Seville oranges, or grapefruit.
Morning dose: take ____ 10 mg tablets and ____ 20 mg tablets.
Evening dose: take ____ 10 mg tablets and ____ 20 mg tablets.
3. The non-shaded rows indicate the days in which you will take your BAY 1895344 tablets.
4. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
5. If you vomit after taking BAY 1895344, do not retake the dose. Take your next dose at the originally scheduled time.
6. If you have any comments or notice any side effects, please record them in the Comments column.
7. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
8. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.

Day	Date	Time of morning dose	# of tablets taken		Time of evening dose	# of tablets taken		Comments
			10 mg	20 mg		10 mg	20 mg	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

PATIENT'S MEDICATION DIARY – CYCLE 2

Today's date _____ Agent _____ BAY 1895344 _____

Patient Name _____ (initials acceptable)

Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. **You will take BAY 1895344 tablets three times with each radiation treatment. Take the tablets 12 hours apart, starting at least 1 hour before and no more than 6 hours before each radiation treatment.** Take BAY 1895344 tablets one (1) hour before or two (2) hours after a meal with approximately 240 mL (approximately 8 ounces) of water. Do not consume grapefruit juice, Seville oranges, or grapefruit.
Morning dose: take _____ 10 mg tablets and _____ 20 mg tablets.
Evening dose: take _____ 10 mg tablets and _____ 20 mg tablets.
Note: You will take a total of nine (9) doses of BAY 1895344 during your radiation therapy.
3. Your doctor will tell you which days to take BAY1895344 based on your radiation treatment schedule.
4. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
5. If you vomit after taking BAY 1895344, do not retake the dose. Take your next dose at the originally scheduled time.
6. If you have any comments or notice any side effects, please record them in the Comments column.
7. Avoid prolonged exposure to the sun and wear protective clothing and sunscreen when out in the sun.
8. Please bring this form and your bottles of BAY 1895344 tablets when you return for each appointment.

Date and time of **first radiation fraction**: _____

Three doses of Bay 1895344 surrounding radiation treatment #1:

Day	Date	Time of morning dose	# of tablets taken		Time of evening dose	# of tablets taken		Comments
			10 mg	20 mg		10 mg	20 mg	
1								
2					You will not take an evening dose of BAY 1895344			

Date and time of **second radiation fraction**: _____

Three doses of Bay 1895344 surrounding radiation treatment #2:

Day	Date	Time of morning dose	# of tablets taken		Time of evening dose	# of tablets taken		Comments
			10 mg	20 mg		10 mg	20 mg	
1								
2					You will not take an evening dose of BAY 1895344			

Date and time of **third radiation fraction**: _____

Three doses of Bay 1895344 surrounding radiation treatment #3:

Day	Date	Time of morning dose	# of tablets taken		Time of evening dose	# of tablets taken		Comments
			10 mg	20 mg		10 mg	20 mg	
1								
2					You will not take an evening dose of BAY 1895344			

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX E FUNCTIONAL ASSESSMENT OF CANCER THERAPY FOR PATIENTS WITH HEAD AND NECK CANCER (FACT-H&N), VERSION 4

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>PHYSICAL WELL-BEING</u>	Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4

GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4

H&N7	I can swallow naturally and easily	0	1	2	3	4
						
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
						
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
						
H&N 10	I am able to communicate with others	0	1	2	3	4
						
H&N 11	I can eat solid foods	0	1	2	3	4
						
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4
						

APPENDIX F PBMCS BLOOD SAMPLES REQUISITION FORM

SECTION 1

DATE OF SHIPMENT:	
SITE NUMBER:	
PATIENT NUMBER:	
PATIENT INITIALS:	
INVESTIGATOR:	

SECTION 2

SITE CONTACT (NAME):	
PHONE NUMBER:	
E-MAIL:	

SECTION 3

Ensure that the specimen labels include the following information: protocol ID, patient ID and initials, specimen type (PBMCS), collection time point (HH:MM) and collection date (MM-DD-YY).	
☐ Prior to 1 st Tx (Baseline)	☐ Week 2 ☐ Week 5 (during RT)
☐ 6 months	☐ 12 months
# of specimens shipped: _____	
Specimen Collected (two 8.5 ml ACD yellow top tubes) @ _____ am/pm on ____/____/____	

SECTION 4

Date of Shipment	
Ship to: Cancer Pharmacokinetics and Pharmacodynamics Facility UPMC Hillman Cancer Center Room G28 Hillman Research Laboratories 5117 Centre Avenue Pittsburgh, PA 15213	

