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Phase I/II Study of M7824 plus curative intent re-irradiation with Stereotactic Body Radiation Therapy (SBRT) in patients with local-regionally recurrent head and neck squamous cell carcinoma

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1. OBJECTIVES

1.1 Primary objective of Lead In

- To evaluate the safety, tolerability and feasibility of M7824 when administered together with SBRT reirradiation.

1.2 Primary objective of Phase 2

- To evaluate the progression-free survival (PFS) rate of M7824 plus SBRT reirradiation at 1 year

1.3 Secondary objectives

- To evaluate the overall response rate by RECIST or RECIST 1:1
- To evaluate the 1- year locoregional control (LRC), locoregional failure-free survival (LFFS), distant metastasis (DM) and overall survival (OS) rates
- To evaluate acute and late toxicity using Common Terminology Criteria for Adverse Events (CTCAE)-v5.0
- To evaluate fibrosis-related toxicities and functional outcomes
- To evaluate Patient Reported Outcome (PRO) measures of symptoms using MD Anderson Symptom Inventory (MDASI).
- To evaluate volumetric tumor regression rate and MRI kinetic biomarkers after M7824 plus SBRT
- To compare Quality-Adjusted-Life-Years (QALY) between M7824 plus SBRT reirradiation and historic SBRT reirradiation control

1.4 Exploratory Objectives

Biomarkers will be accessed in the tumor and blood samples and correlated with clinical outcomes and toxicity. Correlative tissue studies include but are not limited to profiling of the tumor immune microenvironment by IHC and multiplex immunofluorescence analyses (mIF) including quantitative assessment of CD8 T cells and PD-L1 expression levels, immune gene expression signatures by NanoString or HTG, target DNA sequencing to access tumor mutational burden, detailed assessments of immunocyte populations and functional markers by multicolor flow cytometry, and other biomarkers that may emerge to be important related to the use of the proposed agent. Blood will be collected prior to cycles 1, 3 and at disease progression (3 time points) for evaluation of ctDNA, circulating immune biomarkers of interest including cytokines, and measurements of T-cell activation by flow cytometry. Functional outcome measures include but are not limited to validated clinical grading criteria (Head and Neck-Lymphedema and Fibrosis, HN-LEF)[1,2] and patient-reported measures of head and neck fibrosis (Lymphedema Symptom Inventory Distress Scale, L-SIDS)[3], as well as radiographic dysphagia grade (Dynamic Imaging Grade of Swallowing Toxicity, DIGEST)[4], and cervical range of motion (CROM). Correlative imaging studies include functional and anatomic magnetic resonance imaging (MRI).

2. BACKGROUND AND RATIONALE

Stereotactic Body Radiation Therapy (SBRT) enables precise and focused delivery of ablative dose radiation in a few fractions and is capable of providing durable local-regional control in patients with recurrent head and neck squamous cell carcinoma (HNSCC)[5,6], after a median follow-up of 16.7 months,

the 1-year disease control within the reirradiation field (hereafter referred to as local control) is 84% among 67 patients with recurrent HNSCC treated with SBRT reirradiation at MD Anderson. Although the local control with SBRT reirradiation is promising, recurrences outside the reirradiation field remains problematic, with 1-year regional and distant recurrence rates of 18.2% and 21.2%, respectively. Furthermore, while head and neck reirradiation provides high local control rates, it is associated with severe, long-term treatment related adverse events such as fibrosis and dysphagia, with rates as high as 40%[7,8]. Even with the use of conformal radiotherapy techniques such as intensity modulated radiation therapy (IMRT) or proton therapy, the 2- year rates of ≥ grade 3 toxicity approach 30%[9,10].

Transforming growth factor beta (TGFβ) is a cytokine frequently overexpressed by cancers that promotes epithelial-to-mesenchymal transition and is immune suppressive in the tumor microenvironment. TGFβ suppresses the expression of IFNγ and induces differentiation of immune suppressive Tregs. Notably, co-targeting of TGFβ and immune checkpoints PD-1/L1 or CTLA4 demonstrates greater tumor control than either alone in in vivo models of melanoma[11]. M7824 is a first-in-class bi-functional fusion protein composed of a monoclonal antibody (mAb) against programmed death ligand 1 (PD-L1) fused to a TGFβ "trap". M7824 was well tolerated in patients with heavily pretreated solid tumors and promising clinical activity was seen particularly in HPV-related cancers. In addition to the therapeutic effects of blocking PD-L1, the TGF-β trapping property of M7824 has potential for anti-inflammatory and anti-fibrosis activity [12,13].

In spite of a recent small randomized trial of nivolumab with SBRT versus nivolumab alone in 53 recurrent HNSCC patients not showing an improvement in overall response rate, progression-free and overall survival over nivolumab alone [14], abscopal response in patients with widely metastatic HNSCC has been reported[15]. Furthermore, trials of radiotherapy and immune checkpoint blockade have demonstrated abscopal response in non-irradiated lesions between 10 and 27% of patients with metastatic melanoma [16,17]. Anti-PD1 can also potentiate the radiation effect locally, which is particularly attractive in the proposed population with oligo, loco-regional recurrent disease amenable to radio-ablative re-irradiation, and pre-clinical studies using mouse models demonstrated significantly less radiation-induced inflammation and fibrosis by the concurrent administration of TGF-β inhibitors [18,19].

In summary, rationale for evaluating the combination of SBRT and M7824 in patients with recurrent, previously irradiated HNSCC include: (1) the increasing evidence for radiotherapy to generate antitumor immune response and synergize with PD-L1 inhibitors; (2) the compelling preliminary efficacy and safety data of M7824 in patients with refractory solid tumors; (3) the synergy between co-targeting of PD-1/L1 and TGFβ in the tumor microenvironment; and (4) the anti-fibrotic properties of M7824 due to its anti-TGF-β component to mitigate reirradiation fibrosis/toxicity. These findings support a strong rationale for testing M7824 in combination with SBRT in patients with local-regionally recurrent, previously irradiated HNSCC.

2.1 Introduction

HNSCC account for over 550,000 cases worldwide and 55,000 cases in the U.S. annually, with an estimated 12,000 dying each year from the disease [20]. Radiotherapy, alone or in combination with chemotherapy, is integral to the treatment of many HNSCC, either in the primary management as part of an organ preservation approach or in the adjuvant setting after surgery[21]. Despite improvements in

HNSCC treatment, local-regional recurrence occurs in 15-50% of patients and is the most common cause of death [22-24]. Among survivors, secondary primary HN tumors can occur in up to 40% of patients [25].

Although, salvage surgery is historically the treatment of choice among patients with recurrent or second primary HNSCC after radiotherapy, many have unresectable disease, are medically unfit, or refuse surgery for various reasons, including loss of organ function[26,27]. In these patients, the previous standard-of-care was chemotherapy. Unfortunately, the prognosis with chemotherapy alone is poor, with pooled-analyses showing a median survival of 7.4 months compared to 4.6 months with supportive care alone, with a marginal improvement to 10 months with the addition of cetuximab to platinum-based chemotherapy [24,28 26,29]. Furthermore, prior radiation has been reported as an independently poor prognostic factor in patients receiving systemic therapy for recurrent HNSCC[30].

2.2 Reirradiation

In select patients who are not surgical candidates, reirradiation is a potentially curative treatment option[3,4]. However, head and neck reirradiation is a clinical challenge, and carries a significant risk of severe morbidity and toxicity to nearby normal tissue[5]. Reirradiation with older two-dimensional (2D) and three-dimensional (3D) approaches have yielded modest local-regional control (LRC) rates of up to 50% at 3 years, albeit with serious treatment-related toxicity risks, including 40-60% grade 3 or higher toxicity and up to 20% treatment related deaths [6,9 27,31]. An additional challenge with recurrent HNSCC is the development of tumor radioresistant clones acquired through prior treatment, which may limit the effectiveness of subsequent therapy [26,32]. Proposed retreatment strategies to reduce reirradiation toxicity and overcome tumor radioresistance include the use of conformal radiotherapy techniques, altered fractionation strategies and/or the addition of systemic radiosensitizers. More-recently, the combination of immunotherapy and radiotherapy has demonstrated synergy[33].

2.3 Stereotactic Radiotherapy

Modern highly conformal radiotherapy techniques, such as intensity modulated radiation therapy (IMRT), proton therapy, and SBRT are attractive options for those with recurrent HNSCC. Retrospective and prospective reports have demonstrated improved local disease control and survival compared with use of 2D and 3D radiotherapy [34-36]. Our institution recently published the largest series of 207 patients reirradiated with IMRT with curative intent. The 2-year LRC and overall survival (OS) rates were 65% and 57%, and 5-year rates were 49% and 42%, respectively [9]. The median survival was 25.1 months overall and 22.5 months for patients with SCC histology. The grade 3 or higher treatment related morbidity was 32% at 2 years and 48% at 5 years. Multivariate analysis showed that retreatment volume >50 cc (P=0.001) and use of platinum based chemotherapy (P=0.02) were associated with higher late grade 3 toxicity rates[9]. Similarly, our recently published study of 60 patients reirradiated with proton beam showed 2 year LRC and OS rates of 73% and 70%, respectively. The 2 year late grade 3 or higher toxicity rate was 26% [10].

SBRT enables precise and focused delivery of ablative dose radiation in a limited number of treatments (typically 1-5) and has become a standard approach in several disease sites such as lungs, brain and prostate [37-41]. Logistical and financial advantages of SBRT over existing conformal radiotherapy modalities include fewer number of treatments, shorter treatment duration (typically <2 weeks vs 6-7

weeks), fewer clinic visits and/or lost work hours. Clinical advantages of SBRT include reduced exposure of nearby normal tissues to reirradiation dose, use of ablative/high doses to confer additional mechanisms of cell kill, superior immune elicitation compared with standard fractionation, and a shorter interval to systemic therapy that benefits a population at high risk for metastatic development[42].

A growing body of literature demonstrates SBRT for HNSCC reirradiation can provide durable local-regional control and is well tolerated relative to conventionally fractionated RT [37-41 *29-30.*] Retrospective and prospective studies from the University of Pittsburgh and others demonstrate SBRT is associated with late grade 3 toxicity rates between 10% and 30% when delivered with every other day (QOD) frequency. The 2-year local control rates were 35-65% and 1-year OS rates were 30-60%[*43,44 41,45,46*]. Our recently reviewed institutional experience of 101 patients with recurrent HNSCC reirradiated with SBRT to a median dose of 45 Gy in 5 fractions (delivered QOD) showed a 1-year local control rate of 87%, with a median follow-up of 15.9 months (unpublished data). Patient reported quality of life outcomes showed lower symptom burden associated with SBRT[47]. No difference in disease control rate or progression free survival for recurrent versus second primary tumors in a previously radiated field was noted on our institutional data, which is consistent with other published experiences[9,48,49].

Although local control with SBRT reirradiation is promising, recurrences outside the reirradiation field remains problematic. Our data demonstrates 1- and 2- year regional recurrence rates of 16% and 24%, respectively, and 1- and 2-year distant recurrence rates of 16% and 28%, respectively (manuscript in progress). Furthermore, head and neck reirradiation is associated with severe, long-term treatment related adverse events, with rates of severe fibrosis/dysphagia as high as 40%[7,8]. Even with the use of conformal IMRT and proton radiotherapy, 2-year grade 3 or higher toxicity rates approaches 30%[9,10].

2.4 Checkpoint Inhibitors in Head and Neck Cancer

Cancer immunotherapy is based on the premise tumors can be recognized as foreign invaders and effectively killed by an activated immune system. However, it is also recognized that tumor-infiltrating lymphocytes (TILs) in proliferating cancers can be rendered ineffective by the tumor microenvironment. The pathogenesis and progression of HNSCC may therefore be facilitated by local immunosuppressive alterations. Down-regulation of T cell function has been reported in HNSCC. And is thought to be mediated by multiple mechanisms. These include increased expression of the programmed death receptor ligand-1 (PD-L1) in tumor cells, suppression of TIL activity by tumor associated fibroblasts, production of immune suppression factors such as TGF-β, and co-stimulation of B7-CD28 family molecules[50 51,52]. Recurrent HNSCC can be particularly immunosuppressive, with impaired natural killer (NK) activity, reduced antigen-presenting function, impairment of tumor infiltrate lymphocytes (TILs), and increased population of suppressive Treg[51,53-56].

PD-L1 is one of two specific ligands for the programmed death receptor-1 (PD-1), a transmembrane protein and a member of the CD28 family of T-cell co-stimulatory receptor expressed on activated T cells. PD-L1 has been shown to down-regulate T-cell activation upon binding to PD-1. PD-L1 expression on tumor cells has been correlated with increased tumor aggressiveness, development of distant metastasis and decrease survival[57]. Several clinical trials of anti-PD-L1 therapy have demonstrated clinical activity of immunotherapy in patients with heavily pre-treated, recurrent/metastatic HNSCC. Several clinical

trials (Keynote 12; Keynote 55) have demonstrated an ORR of 11-22% and 1 year OS of 38% (Keynote 12) with use of single agent anti-PD1 or anti-PD-L1 monoclonal in those with recurrent metastatic HNSCC. Importantly, data from a phase III trial (CheckMate 141) demonstrated that anti-PD-1 improved survival of patients with platinum-refractory recurrent or metastatic HNSCC compared to standard of care chemotherapy and reduced the risk of death by 30% (HR 0.70, 96% CI 0.51-0.96) compared to single agent methotrexate, docetaxel or cetuximab of investigator's choice[12]. The 1-year OS was 36% with anti-PD-1.
More recently results of CheckMate-048 published in abstract form demonstrated that anti-PD1 as a single agent is non-inferior to chemotherapy with cetuximab in the first line setting and superior to chemotherapy with cetuximab in patients with a PD-L1 combined positive score of at least 1%, supporting anti-PD1 as a standard of care first line therapy for patients with recurrent/metastatic HNSCC[58].

TGF-β plays a critical role in regulation of epithelial proliferation and differentiation, and disruption of TGF-β signaling is common in HNSCC[59]. TGF-β overexpression in the tumor microenvironment promotes tumor immune evasion and metastasis and is associated with poor prognosis. TBF-β is a critical mediator of epithelial-to-mesenchymal transition to promote immune evasion and metastasis of HNSCC. Moreover, TGF-β is immunosuppressive in the tumor microenvironment. It decreases activity of Anaphase-promoting complex (APC) and NK cells, decreases T cell proliferation, facilitates recruitment of Tregs, promotes M2 polarization of TAM and angiogenesis by increasing VEGF production by TAM. TGF-β also mediates cell cycle quiescence and resistance to chemotherapy in squamous cell carcinomas[60] . TGF-β is also implicated as a driver of numerous fibrotic diseases through stimulation of collagen deposition, including the fibrosis induced by radiotherapy[61]. As a consequence of its pathophysiological roles in cancer and fibrotic syndromes, numerous TGF-β inhibitors have been developed[62].

2.5 M7824: Rationale For Combination PD-L1 and TGF- β-inhibition

M7824 is a first-in-class bifunctional fusion protein composed of a mAb against PD-L1 fused to a TGFβ "trap". M7824 consists of the PD-L1 antibody linked to the extracellular domain of 2 TGFBRII molecules[63]. Synergy between TGFβ inhibition and anti-PD-L1 has been demonstrated in animal models, supporting the combination into one molecule[11]. M7824 blocks the immunosuppressive effects of TGFβ on NK cell function[63]. M7824 has also been shown to reverse EMT, a mechanism of immune evasion, in lung cancer[64]. M7824 also demonstrated synergy with radiotherapy and enhanced the abscopal effect. In phase 1 clinical trials, the maximal tolerated dose could not be defined with the highest dose level tested being 20mg/kg every 2 week[13]s. Based upon pharmacokinetic data, a dose of 1200 mgs every 2 weeks has been chosen for further development.

In a phase I 3+3 dose escalation and expansion study of 19 patients, M7824 was well tolerated in patients with heavily pretreated solid tumors and promising clinical activity was seen. Responses observed include a complete response in a patient with cervical cancer, 2 partial responses in anal and pancreatic cancer, and prolonged stable disease in 6 subjects[13].

Based upon a total of 377 patients in expansion cohorts, M7824 administration has been associated with infusion-related reactions, immune mediated adverse events and skin lesions with hyperkeratosis, which is a known drug class effect of TGF-β inhibitors. The most frequent treatment related adverse events of any grade were pruritus (11.4%), rash (13%), diarrhea (9%), asthenia (10.3%), fatigue (7.7%), decreased

appetite (5.6%) and anemia (6.1%). Of the 377, 58 subjects (15.4%) experienced at least 1 grade 3 or greater adverse event. These included anemia, rash, colitis, diarrhea, vomiting, lipase increase, ALT increase, fatigue, acute kidney injury, hypophosphatemia and keratoacanthoma (0.5%). One subject with pancreatic cancer had a grade 4 lipase increase and 1 subject died from grade 5 hemolysis, thrombocytopenia and dyspnea.

Additional details regarding the clinical development of M7824 as well as adverse events are provided in the attached Investigator's Brochure.

2.6 M7824 and SBRT

Recurrences outside the reirradiation field remain problematic. Furthermore, while head and neck reirradiation offers the promise of durable disease control, it is associated with severe, long-term treatment related fibrosis and dysphagia[7,8].

The combination of targeted SBRT and immune checkpoint inhibition offers the potential to control the local recurrence using smaller reirradiation fields while mitigating disease recurrence regionally and distantly. Studies have shown their combination have been improved antitumor activity compared to either therapy alone[16]. Recent trials of radiotherapy and immune checkpoint blockade demonstrate abscopal response in unirradiated lesions in 10-27% of patients with metastatic melanoma[17]. In addition to blocking PD-L1, M7824 TGF-β trapping properties have anti-inflammatory and anti-fibrosis activity[12]. Pre-clinical studies using mouse models demonstrated significantly less radiation-induced inflammation and fibrosis when concurrent administered with TGF-β inhibitors[18,19].

Therefore, there is a strong impetus to evaluate the combination of SBRT and M7824 in patients with recurrent, previously radiated HNSCC based on the following rationale: (1) evidence for radiotherapy to generate antitumor immune response and synergize with PD-L1 inhibitors; (2) compelling preliminary efficacy and safety data of M7824 in patients with refractory solid tumors; and (3) M7824 anti-fibrotic properties from its anti-TGF-β component.

2.7 Functional and patient reported outcome measures

An unanswered question is how specific immune checkpoint blockade and radiotherapy toxicities can impact health-related quality of life (HR-QOL) and function. A few studies have suggested that HR-QOL scales, together with clinical data, might improve survival prediction [65-67] [19,20,21]. While PRO and quality of life and symptom burden measures of this population are of great interest, there are few prospective studies that assess the impact of SBRT and checkpoint inhibitor blockade. In this setting, an additional purpose of this study is to analyze functional and patient reported outcome measures with the combination of M7824 plus SBRT reirradiation for recurrent HNSCC. To minimize survey burden and personalize PROs to expected patterns of toxicity, the PRO bundle differs by site of recurrence (mucosal, neck, skull base anterior v non-anterior) as detailed in Table 1.

3. PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients with histologically documented local-regional recurrent squamous cell carcinoma of the head and neck, or second primary squamous cell carcinoma of the head and neck;

Patients must be willing to undergo research biopsy for tissue collection at baseline and at disease progression;

Previous receipt of at least 30 Gy of radiation for HNSCC with overlapping fields;

Not eligible or poor candidate or patient refusal of surgery for recurrence;

Evaluable disease apparent on imaging (MRI or CT);

1 to 3 sites of recurrence (<60 cm^3 per site, total volume <100 cm^3);

Age ≥ 18 years;

Eastern Cooperative Oncology Group (ECOG) = 0, 1, or 2;

Adequate hematologic function defined as follows:

WBC ≥ 2000/µL;
Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
Platelets ≥ 100,000 cells/mm^3;
Hemoglobin ≥ 9.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable.

Adequate renal function as follows:

Serum creatinine ≤ 1.5 mg/dl or creatinine clearance (CC) ≥ 50 ml/min determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$

CCr female = 0.85 x (CrCl male).

Adequate hepatic function as follows:

Total bilirubin ≤ 1.5 x ULN (except patients with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL);

AST or ALT ≤ 3 x the upper limit of normal.

Negative serum pregnancy test for women of childbearing potential and confirmation within 24 hours of first dose of study drug.

3.2 Exclusion Criteria

Presence of distant metastases;

Less than six-month disease free interval from end of prior radiotherapy to the head and neck;

Prior receipt of anti-PD-1/L1 therapy.

Patients who are pregnant or breast feeding;

Clinically significant uncontrolled major cardiac, respiratory, renal, hepatic, gastrointestinal or hematologic disease but not limited to:

Symptomatic congestive heart failure, unstable angina, or cardiac dysrhythmia not controlled by pacer device; myocardial infarction within 3 months of registration.

Active autoimmune disorder or immunosuppression (including HIV, but excluding endocrine abnormalities that are controlled with replacement medications);

Active viral hepatitis;

Steroid therapy of greater than prednisone 10 mgs a day or equivalent;

Prior history of invasive non-head and neck cancer within two years, with the exception of screen detected prostate cancer treated with observation only, basal cell and squamous cell carcinoma of the skin, and micro-invasive resected cervical carcinoma.

4. STUDY SCHEMA

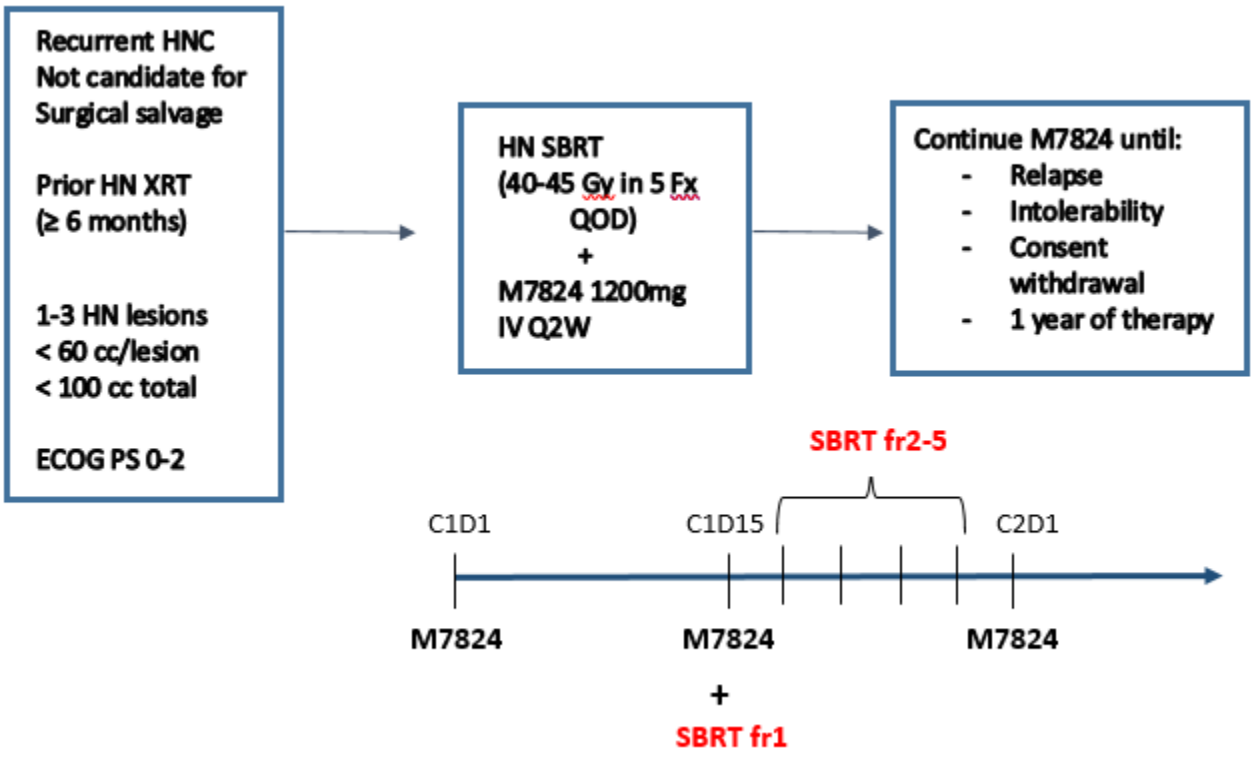

Fig 1. Study Schema

Abbreviations: **HNSCC** = head and neck squamous cell carcinoma; **XRT** = Radiotherapy; **PROs** = Patient Reported Outcomes; **SBRT** = Stereotactic Body Radiation Therapy

5. STUDY EVALUATIONS

Table 1 summarizes the pretreatment (initial screening, baseline measures prior to enrollment), on treatment, post-treatment phases of the trial, and the evaluations that would be required during these phases.

TABLE 1: Summary of Study Evaluations

Procedure	Screening	On-Treatment	First Follow-up	Follow-Up
	Day -28 to D1	C1-C12, D1,D15 ($^{+}$/- 3 days), Q28D cycles	90 days after last dose of M7824 ($^{+}$/- 14 days)	Q6 mo. Yr. 2-5 ($^{+}$/- 28 days)

Informed consent	X			
Medical history	X			
Physical exam	X	X	X	X
Vital signs	X	X	X	X
Dermatological exam	X	Every 3 mo.	X	X
Performance status	X	X	X	X
Review of prior radiation fields	X			
CT or MRI of neck	X	3, 6, 9, 12 mo.		18, 24 mo.
CT scan of chest[d]	X	3, 6, 9, 12 mo.		18, 24 mo.
BMP, creatinine, CBC diff, Mg, hepatic function	X	X	X	As clinically indicated
Lipase, amylase, TSH, free T4	X	X (every other cycle)	X	As clinically indicated
HBsAg, HCV Ab	X			As clinically indicated
Preg Test for childbearing women	X	Every 3 mo.		As clinically indicated
12 lead EKG	X			
Adverse event evaluation	X	X	X	
Tumor biopsy [a]	X			At progression
Blood (serum)for PK [b]		X		At progression

Blood (serum)for ADA [b]		X		At progression
Blood for biomarker analyses [c]		X	At progression	At progression
All patients				
Medical Photo	X			Q6 mo. Yr. 2-5
MDASI-HN	X	3, 6, 12 mo.		18, 24 mo.
EQ-5D	X	3 mo.		24 mo.
Radiation Swallow Pathway *(all mucosal, all neck, non-anterior SB)*				
Swallowing clinic/Therapy	X			
MBS	X	3-6 mo.		18-24 mo.
PSS-HN	X	3-6 mo.		18-24 mo.
CROM + HN-LEF	X	3-6 mo.		18-24 mo.
MDADI	X	3-6 mo.		18-24 mo
LSIDS-HN				
Mucosal primary only				
Video-Strobe +/-2 wks	X	3-6 mo.		18-24 mo.
Anterior skull base only				
ASBQ	X	3-6 mo.		18-24 mo

Footnote: Radiation Swallowing Therapy Pathway includes all patients with mucosal site of recurrent disease, all with cervical lymph node recurrence, and non-anterior skull base, MBS + MDADI, LSIDS-HN and CROM/HN-LEF occurs at baseline, 3-6 months and 18-24 months after end RT; assessment with SLP post-RT videostroboscopy and recommended on same schedule for mucosal primaries; SLP therapy visits are at clinician discretion but typically include a minimum of pre, during week 1, and end RT during week 2, and 6 weeks evaluation may include FEES particularly if laryngeal primary tumors.

a. Mandatory tumor biopsies will be collected prior to treatment and at progression, refer to section 10.2 for details on tumor collection.
b. Blood samples of approximately 3.5 mL will be drawn prior to and immediately after M7824 infusion for doses 1 and 3 (cycle 1 day 1 and cycle 3 day 1), and only prior to infusion for cycle 2 day 1 and cycle 6 day 1 OR end of treatment (whatever comes first) for analysis of pharmacokinetics. Blood samples will also be collected prior to infusion of cycle 1 day1 and cycle 6 day 1 or end of treatment (whatever comes first) for analysis of ADA.
c. Blood (2 x 10 cc streck, 2 x 10 cc EDTA plasma and 2 x 10 cc heparin PBMCs) will be collected for biomarker analysis prior to infusion on C1D1, C1D15, C2D1, C2D15, C3D1, C6D1, and C12D1, refer to section 10.2 for details.
d. CT abdomen and pelvis and/or MRI brain should be ordered if clinically indicated at the discretion of the treating physician.

Vital signs include HR, BP, and temperature; all laboratory assessments at baseline and on treatment may occur within 72 hours of drug administration; windows for disease assessment by imaging and QOL endpoints are +/- 7 days.

For female participants of childbearing potential, a urine or serum β-human chorionic gonadotropin test will be performed according to the Schedule of Assessments. Participants who are not WOCBP are exempted from pregnancy testing, but the reason must be documented.

5.1 Details regarding function and quality of life endpoints

The PRO-QOL will consist of a battery of previously validated HR-QOL and Symptom Inventory questionnaires [60-68]. This includes: M.D. Anderson Dysphagia Inventory (MDADI), M.D. Anderson Symptom Inventory-Head and Neck (MDASI-HN), M.D. Anderson Symptom Inventory – Brain Tumor (MDASI-BT) for skull base only, Anterior Skull-Base Questionnaire (ASBQ) for skull base only, Brief Fatigue Inventory (BFI), EuroQol (EQ5D), Performance Status Scale For Head and Neck Cancer Patients (PSS-HN), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP). These questionnaires will be performed in person by mail or by phone or by secure electronic methods. The research coordinator will notify the patient via telephone, email or via electronic notification 1-3 weeks after the questionnaire is sent to remind the patient and give them the option of performing the survey by other means. During patient follow-up period, HR-PRO will be assessed at the completion of reirradiation, and subsequently during follow up visits for all patients up to 24-months post reirradiation (Table 2).

Clinician-rated, fibrosis-related measures will be conducted according to the schedule in Table 1. Clinician-rated measures are standard, brief procedures incorporated into the supportive care visits of patients receiving radiotherapy for HNSCC at MD Anderson Cancer Center. In addition to these functional measures, patients may be eligible for dual consent for an imaging study with serial MRI (separately funded) to quantify soft tissue parameters that may serve as an objective and quantitative imaging marker of fibrosis. PRO and functional outcome schedules are harmonized.

Cervical Range of Motion (CROM): A goniometer will measure CROM (degrees) to assess active cervical

spine ROM. Five core CROM measures will be collected, including cervical extension, sagittal plane at rest, lateral flexion (left/right), coronal plane at rest, and lateral rotation (left/right). The primary CROM measure of interest is cervical extension. Cervical extension measures are highly reliable (ICC=.90). Average extension measures in healthy adults aged 60 to 69 range from 57 degrees in males (SD: 10.5) to 65 degrees in females (SD: 13.3). Cervical extension measures decrease by approximately 5 degrees for each decade of life.[68]

Lymphedema/Fibrosis Grading: Clinician-grading of lymphedema/fibrosis will be conducted according to the published Head and Neck-Lymphedema Fibrosis (HN-LEF)[1,2] per physical examination of the patient. Clinical grading is a brief assessment that can be completed in <5 minutes.

Modified Barium Swallow (MBS) Studies: The *MBS* (also known as a videofluoroscopic swallowing study) is a dynamic, radiographic study used to measure oropharyngeal swallow physiology, aspiration and/or pharyngeal residue.[69] Digital videos from SOC MBS will be scored by a trained speech pathologist blinded to patient, study, and follow-up interval using methods including the *Dynamic Imaging Grade for Swallowing Toxicity (DIGEST)*[70].

M.D. Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) is a patient-reported outcome questionnaire designed to measure severity or burden of systemic and head and neck (HN) specific symptoms and their interference with or effect on patients' daily functioning. This 28-item multi-symptom inventory includes 13 core items ("systemic symptoms": pain, fatigue, sleep, *etc*.), nine

HN-specific items ("local symptoms": dry mouth, mucus, shortness of breath, taste, *etc*.), and six interference items (activity, work, relations, *etc*.). The core MDASI items have been validated for use in cancer patient populations regardless of the specific diagnosis or type of therapy and thus can be used to compare overall burden of disease between different types of cancer[71]. The HN-specific items were validated internally with regard to construct and concurrent validity in HN cancer patients.[72,73] MDASI includes the following symptom items for possible IO related toxicity: pain, fatigue, skin pain/burning/rash, shortness of breath, dry mouth, appetite, and nausea. Internal consistency reliability is high in the core, HN-specific, and interference items (Cronbach's alphas of 0.72-0.92). Validated linguistic translations (Chinese, French, German, Greek, Italian, Spanish, and Turkish) of the MDASI-HN may be administered to non-English speaking participants.

EuroQOL-5 Dimensions - 5L (EQ5D-5L) is a modified version of the widely used EuroQOL 5 Dimension. (Herdman, M. et al. 2011). The 6-item EQ5D-5L questionnaire is used to measure generic quality of life. The EQ5D-5L descriptive system measures five levels of severity in each of the existing five dimensions that includes mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The questionnaire also contains a Visual Analog Scale, by which respondents can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status).

M.D. Anderson Dysphagia Inventory (MDADI) is a written questionnaire to evaluate dysphagia-specific QOL in H&N cancer patients.[74] The 20-item MDADI questionnaire quantifies an individual's global, physical, emotional, and functional perceptions of his or her swallowing ability. In an internal validation in 100 patients with HNC, concurrent validity was found to be moderate by comparison with the

Performance Status Scale for Head and Neck Cancer Patients (Spearman correlation, 0.47-0.61). Correlation with the physical functional subscale (Spearman correlation, 0.40) and emotional subscale of SF-36 (36-Item Short Form Survey) (Spearman correlation, 0.36) demonstrated convergent and divergent validity, respectively, of the MDADI. Test-retest reliability (physical, 0.86; emotional, 0.88; functional, 0.88) and internal consistency reliability (overall Cronbach's alpha, 0.96) were sound.

Lymphedema Symptom Intensity and Distress Survey – Head and Neck (LSIDS-H&N) [3] is a 64-item instrument designed to assess lymphedema symptoms in head and neck cancer patients. Survey items were selected to address six domains (head and neck-specific functioning, systemic symptoms, psychosocial issues, altered sensation symptoms, neck-shoulder musculoskeletal/skin symptoms, and miscellaneous symptoms) identified by an expert panel. Preliminary testing of LSIDS-H&N demonstrated both feasibility and readability.

Anterior Skull Base Questionnaire (ABSQ) is a validated and widely utilized 35-item questionnaire designed as a standardized tool for assessment of quality of life concerns unique to patients with anterior skull base tumors (Gil Z, Abergel A, Spektor S et al. Arch Otol Head Neck Surg. 2003; 129(12):1303-1309. The questionnaire consists of 35 questions divided into 6 domains covering the areas of performance, physical function, vitality, pain, specific symptoms (e.g. taste, smell, nasal function and visual function) and influence on emotions.

6. THERAPY

6.1 Radiotherapy

6.1.1 Simulation

All patients will undergo CT simulation. Patients will be simulated in the supine position. Patients must be immobilized with a customized Klarity AccuCushion (Klarity Medical Products, Newark, OH), a thermoplastic head neck and shoulder mask (Orfit Industries America, Wijnegem, Belgium), and a customized bite-block attachment fixated to the thermoplastic mask. The Klarity AccuCUsion is shaped to the veretx and sides (mastoid process and temple) of the head, and along the curvature of trapezius and sternocleidomastoid muscles of the neck to shoulders. This creates a custom posterior cup for indexing of the thermoplastic mask and minimizes mask-air space. A preheated moldable bite-block (Precise Bite, Civico, Coralville, IA) is then conformed to the patient's upper teeth. The bite-block contains two outward attachments that are indexed to the warm thermoplastic mask and secured by snapping a small backing plate to the mouth piece from outside the mask. Six IR passive reflection balls are placed on the mask before CT scans for ExacTrac use during treatment for in-room alignment and motion tracking [75].

For each patient, a simulation CT scan will be acquired with 1 mm slice thickness and coregistered in the treatment planning system (Pinnacle, version 9.8, Philips Medical Systems, Andover, MA) with diagnostic MRI and/or PET-CT, as well as treatment planning MRI and/or DECT and/or PET-CT images obtained with patient immobilized with the CMB.

6.1.2 Contouring and Treatment Planning

Each patient will get a CABI/PTC-MRI and either a CABI PET CT or dual energy CT at the treating physician's discretion, which will be fused with the simulation CT to assist with target delineation and contouring.

The gross target volume (GTV) and critical structures will be contoured. Based on our published outcomes with the CMB system, a 2–4 mm PTV margin should added to the target volume by the attending physician (Wang He, Wang Congjun, Tung S, et al. J Applied Clin Med Physics 17(3): 1-10. 2016).

6.1.3 Radiation Dose Specifications

SBRT will be delivered to a total prescription dose of up 40-45 Gy to 5 fractions prescribed to PTV delivered every other day for an overall treatment time of two weeks. SBRT will be performed using either 6 MV photon beams on Varian TrueBeam STx system (Varian Medical Systems, Inc., Palo Alto, CA) with high definition (2.5 mm) leaflets or on the Accuray CyberKnife M6 (with or without HDI) (Accuray, Inc., Sunnyvale, CA).

The prescribed dose should cover at least 95% of the PTV. No more than 2% of PTV receives < 92% of the prescribed dose, except in the area adjacent to critical structures including spinal cord and brainstem, in which optimal sparing of these structures could not be achieved. In such instances, no more than 5% receives <80% of the prescribed dose may be permitted.

6.1.4 Treatment Verification

ExacTrac and cone beam CT will be used for each SBRT treatment.

6.1.5 Normal Tissue Dose Constraints

The compliance criteria listed in Table 6.16 below will be used to evaluate each case. The per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. Deviation Unacceptable category are plans that do not meet the Variation Acceptable limits and are considered suboptimal and additional treatment planning optimization is recommended to avoid protocol deviation.

Table 6.1.6 Planning Target Volume and Critical Normal Tissue Constraints and Compliance Criteria for SBRT in 5 Fractions

Structure Name	Dosimeric Parameter	Per Protocol Dose	Variation Acceptable
PTV	D95%* (Gy) V40-45 Gy (%)	40-45 Gy ≥95 %	>35-50 Gy

Cochlea	Dmax** (Gy)	< 18 Gy	<23 Gy
Optic nerve(s)	Dmax** (Gy) V21 Gy (cc)	<15 Gy	<23 Gy <0.2 cc
Optic chiasm	Dmax** (Gy)	< 12 Gy	<18 Gy
Brainstem	Dmax** (Gy) V21 Gy (cc)	<15 Gy	<23 Gy <21 Gy
Temporal lobe	Dmax** (Gy) V25 Gy (cc)	<20 Gy	<27 Gy <1.0 cc
Spinal Cord	Dmax** (Gy)	<12 Gy	<15 Gy
Brachial Plexus	Dmax** (Gy) V27 Gy (cc)	<25 Gy	<32 Gy <3.0 cc

*D95% (Gy) = dose to 95% of volume; **Dmax = maximum dose to 0.03 cc of volume

Table 6.1.7 Recommended dose acceptance criteria for other normal tissue (not overlapping PTV), but not to be used for plan score

Structure Name	SBRT (5 fractions) Recommended dose acceptance criteria
Parotid(s)	As low as possible; Mean dose <15 Gy
Carotid(s)	As low as possible; Max dose <30 Gy; <5% hot spots in volume overlapping PTV
Larynx	As low as possible; Mean dose <10 Gy; Max dose <15 Gy
Mandible	As low as possible; Mean dose <10 Gy; Max dose <30 Gy
Esophagus	As low as possible; Mean dose < 10 Gy; Max dose < 30 Gy
Oral Cavity	As low as possible; Mean dose < 10 Gy; Max dose < 20 Gy
Pharyngeal Mucosa	As low as possible; Mean dose < 10 Gy; Max dose < 20 Gy

6.2 M7824 Systemic Therapy

6.2.1 Description of the Investigational Medicinal Product

The M7824 Concentrate for Solution for Infusion (liquid formulation) is packaged at a 10 mg/mL concentration in USP / Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL). The vials are closed with rubber stoppers in serum format complying with USP and Ph Eur with an aluminum crimp seal closure.

6.2.2 Dosage and Administration

A cycle is defined as 28 days with M7824 administered on days 1 and 15.

Participants will receive an IV infusion of M7824 at a dose of 1200 mg over 1 hour (-10 minutes/+20 minutes, ie, over 50 to 80 minutes) on days 1 and 15.

Modifications of the infusion rate due to infusion-related reactions (IRRs) are described in Section 6.2.3. In order to mitigate potential IRRs, premedication with an antihistamine and with acetaminophen approximately 30 to 60 minutes prior to each dose of M7824 is mandatory for the first 2 infusions. Premedication is optional and at the discretion of the Investigator after the second infusion. If Grade ≥ 2 infusion reactions are seen during the first 2 infusions, then premedication should not be stopped. Steroids as premedication are not permitted. Special precautions for monitoring of participants and management of IRRs/hypersensitivity, including modifications of the infusion rate and stopping of study drug are described in Section 6.2.3.

6.2.3 Management of adverse events attributable to M7824

Adverse drug reactions (ADRs) are defined in this study as any AEs related to study treatment assessed by the Investigator and/or Supporting company EMD Serono. Serious adverse reactions (SARs) are ADRs that are assessed as serious. Questions or concerns with regards to management and/or follow up of ADRs should be discussed with the Medical Monitor.

Immune-related AEs, IRRs, anemia, and potentially TGF-β-mediated skin AEs are managed and followed up in their respective sections. Permanent treatment discontinuation may be recommended, so the relevant section must be reviewed:

- For suspected irAEs, irAE management and guidance is presented below. General management by NCI-CTCAE v5.0 toxicity grading, as per ASCO, is listed below: Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities; Grade 2: study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent); Grade 3: study treatment is generally suspended and the high-dose corticosteroid treatment (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy; Grade 4: in general, permanent discontinuation of study treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.
- IRRs and hypersensitivity reactions guidance are presented below.
- Anemia guidance is presented below.
- Guidance and management for potentially TGF-β-mediated skin AEs are discussed below.

Management of KA and cSCC: Any suspicious skin lesion should be biopsied (excisional biopsy preferred) and surgically removed as clinically indicated. No treatment interruption is required. Any questions or concerns should be discussed with the Medical Monitor

For ADRs related to M7824 that are not covered by the ASCO guideline, follow the guidance below:

- Grade 2 ≥doesn't require treatment modification when clinically manageable.
- Grade 3, M7824 should be permanently discontinued for most of Grade 3 recurrent AEs, except for tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor and clinically manageable Hgb decrease (< 8.0 g/dL).
- Grade 4, discontinue permanently, except for single laboratory values out of normal range that do not have clinical relevance.

Infusion-related Reactions Including Immediate Hypersensitivity

Infusion reaction may vary in manifestation and timing, and signs and symptoms usually develop during or shortly after drug infusion that generally resolve completely within 24 hours of completion of infusion. Infusion reactions like cytokine release syndrome may manifest similar signs and symptoms of immediate hypersensitivity/allergic reaction.

All study treatments will be administered on an outpatient basis. As a routine precaution, for the first 2 infusions, all participants enrolled in this study must be observed for 2 hours post end of infusion, in an area with resuscitation equipment and emergency agents. At all times during M7824 treatment, immediate emergency treatment of an IRR or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions like anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents, should always be available along with equipment for assisted ventilation. If no IRRs are observed during the first 2 infusions, the mandated 2 hours post infusion observation time may be reduced to 60 minutes.

Premedication with an antihistamine and with acetaminophen (eg, 25-50 mg diphenhydramine and 500-650 mg acetaminophen) approximately 30 to 60 minutes prior to each dose of M7824 is mandatory for the first 2 infusions, after which premedication is optional and at the discretion of the Investigator. Steroids as premedication are not permitted. If Grade ≥ 2 infusion reactions are seen during the first 2 infusions, premedication should not be stopped.

An assessment for possible IRR should be triggered based upon the development of specific symptoms within 24 hours of an infusion. These possible IRRs are identified based on a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) and criteria on the timely relationship to an infusion. IRRs are divided into reactions versus signs and symptoms.

- An IRR should be considered when onset is on the day of infusion (during or after the infusion) or the day after the infusion (irrespective of resolution date) for any infusion related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity, and/or Type 1 hypersensitivity.

Signs and symptoms of IRRs and hypersensitivity/allergic reactions should be considered when onset is on the day of infusion (during or after the infusion) and resolved completely with the end date within 2 days after onset. Signs and symptoms may include but not limited to pruritus, rash, and hypoxemia.

Table 2 Treatment Modification of M7824 for Symptoms of Infusion-related Reactions Including Immediate Hypersensitivity

NCI-CTCAE Grade v5	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by attending Investigator.
Grade 2* – moderate • Therapy or infusion interruption indicated but if responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Stop infusion of the drug caused IRR. • Increased monitoring of vital signs as medically indicated as participants are deemed medically stable by attending investigator. • If symptoms resolve quickly or decreased to Grade 1, resume infusion at 50% of original rate with close monitoring of any worsening otherwise dosing held until resolution of symptoms with mandated premedication for the next schedule. • If worsens to Grade 3 or 4, follow treatment modification guidelines accordingly.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and / or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion caused IRR immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and close monitoring until deemed medically stable by attending Investigator. Hospitalization may be indicated. • Restart the medication taking out the drug that is the cause of IRRs from the next scheduled visit
IV = intravenous, NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event, and NSAIDs = nonsteroidal anti-inflammatory drugs. Once the M7824 infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For Grade 3 or 4 IRRs, M7824 discontinuation is mandated. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded.	

In the event of a Grade 2* IRR that does not improve or worsens after implementation of the dose modifications indicated in

Table (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next infusion, the Investigator may consider the addition of H2 blocker antihistamines (eg, famotidine or ranitidine), in addition to premedication, for select participants. However, prophylactic steroids are NOT permitted. At the next dose, if the participant has a second IRR Grade ≥ 2 on the slower infusion rate, with the addition of further medication to premedication, the infusion should be stopped and the participant removed from treatment.

Hypersensitivity Reaction

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and can be found at https://www.resus.org.uk/pages/reaction.pdf. Participants should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms may include but are not limited to:

- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale / clammy skin
- Cyanosis.

Management of hypersensitivity includes:

1. Epinephrine injection and IV dexamethasone

2. Participant should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately

3. Alert intensive care unit for possible transfer if required.

Prophylaxis of flu-like symptoms

For prophylaxis of flu-like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), eg, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

Management of Immune-related Adverse Events

The spectrum of irAEs is similar for M7824 as compared to other checkpoint inhibitors, in general. irAEs are considered important identified risks for M7824. Effective risk management of these toxicities (irAEs) primarily caused due to inhibiting PD-L1 and PD-1 pathways respectively is based on key recommendations[76]. Participant education for on time reporting of symptoms of potential irAEs and prompt clinical assessment is critical for effective management and quicker resolution of immune mediated toxicities, thus preventing progression into severe forms of toxicity that otherwise may become life threatening and difficult to manage or warrant permanent discontinuation from study.

For treatment management of irAE per NCI-CTCAE v.5 criteria, refer to American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines and National Comprehensive Cancer Network irAE Management Guidelines.

The recommendations for irAE management, in accordance with the joint American Society of Clinical Oncology Clinical Practice Guidelines[77] and National Comprehensive Cancer Network Guidelines.

Treatment of irAEs is mainly dependent upon severity as defined by NCI-CTCAE v5.0. In general, management by NCI-CTCAE v5.0 grading, as per ASCO, is listed below:

- Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent).
- Grade 3: study treatment is generally suspended and the high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) treatment should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.
- Grade 4: in general, permanent discontinuation of study treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

For organ/system specific management guidelines, review ASCO guideline tables in the joint American Society of Clinical Oncology Clinical Practice Guidelines[77] .

Potential TGF-β-mediated Skin Adverse Events

Skin AEs, possibly due to TGF-β inhibition, including hyperkeratosis, keratoacanthomas (KA) and/or cutaneous squamous cell carcinomas (cSCC), are important identified risks for M7824 and are described in this section.
Skin assessments are performed at baseline and every 3 months for all participants (per Schedule of Assessments in Table 1).

A detailed medical history of genetic or iatrogenic skin conditions, skin type, geographical location, occupational or environmental exposure to radiation or chemicals will be queried. For participants experiencing a dermatologic-related AE (hyperkeratosis, KA, or cSCC), initial biopsy with pathology report of initial AE is expected. Additional excisional biopsies of suspicious lesions should occur, and management discussed with the Medical Monitor, as indicated. Dermatology consultation is encouraged for diagnosis, outcome, and follow up.

Anemia

Preclinical testing of M7824 led to classification of treatment-related anemia is an AESI (refer to Investigator Brochure). Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

For new anemia events assessed as treatment related, items queried may include but are not limited to detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated eCRF including details such as concomitant medications, all laboratory data, updated dosing information and recent tumor evaluation scans.

General guidance for anemia management and evaluation:

- Participants must enter the study with Hgb values at least 9 g/dL; routine blood test parameters are required in the Schedule of Assessments.
- All relevant hematologic testing for treatment-related anemias should be done prior to blood transfusion, if clinically feasible.
- If a participant experiences significant anemia (e.g., < 8 g/dL), then the amount of blood to be drawn may be reduced by not taking blood at selected time points for pharmacodynamic biomarkers. The decision to reduce the time points for these biomarkers will be taken by the Investigator in consultation with the Medical Monitor. This will be documented. Blood will continue to be taken as scheduled for safety analyses, PK, and anti-drug antibodies (ADAs).
- Transfusion should be performed at the discretion of the Investigator, based on clinical assessment and considered when participant experiences significant anemia. An attempt should be made to initiate work up (as specified below) for cause of anemia prior to transfusion if clinically feasible to not confound this work up. In general, blood transfusions and erythroid growth factors are permitted for Hgb ≤ 7 g/dL and/or for life-threatening bleeding.

Guidance for evaluation of suspected treatment-related anemias is provided in

Table 3.

Discuss further management with the Medical Monitor for clinically significant treatment related- anemias.

Table 3 Evaluation Guidance of Suspected Treatment-related Anemia Adverse Events

Baseline Anemia Evaluation (Prior to Transfusion, if Feasible)	
Hb and CBC with differential (e.g., MCV, RDW, ANC, hematocrit, reticulocytes counts) Peripheral blood smear for cell morphological assessment Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries: • Coagulation factors (PT, PTT, INR) • Urinalysis • Iron panel (TIBC, ferritin, Fe) • TSH/hormonal panel • Fecal-occult blood testing • Erythropoietin.	
Further Recommendation Based on Suspected Etiology (in Addition to Baseline Anemia Testing)	
Unknown etiology, suspect possible hemolysis	Coombs test, fibrinogen, haptoglobin, d-dimer Consider hematology consultation. Consider blood transfusion at clinical discretion.
Unknown etiology, suspect possible bleeding	Consider blood transfusion at clinical discretion. Consider surgical/interventional radiology consultation. Consider imaging, as clinically indicated (e.g. FAST scan, CT scan, MRI, angiography). Consider endoscopy (upper/lower).
Unknown etiology despite above work-up	Hematology consultation. Consider bone marrow aspiration/morphologic evaluation.
ANC = absolute neutrophil count, Hgb = hemoglobin, CBC = complete blood count, INR = international normalized ratio, LDH = lactate dehydrogenase, LFT = liver function test, MCV = mean corpuscular volume, PT = prothrombin time, PTT = partial thromboplastin time, RDW = red cell distribution width, TIBC = total Iron binding capacity, and TSH = thyroid stimulating- hormone.	

Anemia severity reporting will follow the NCI-CTCAE v5 guidelines as below (

Table 4).

Table 4 Common Terminology Criteria for Adverse Events (CTCAE) Guidelines for Anemia Severity

CTCAE v.5	Grade 1	Grade 2	Grade 3	Grade 4
Anemia Hgb	Hgb < LLN-10.0 g/dL; < LLN-6.2 mmol/L; < LLN-100 g/L	Hgb < LLN-10.0-8g/dL; < LLN-6.2-4.9 mmol/L; < LLN-100-80 g/L	Hgb < LLN-8.0g/dL; < LLN-4.9 mmol/L; < LLN-80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Hgb = hemoglobin and LLN = lower limit of normal. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.				

Alterations in Wound Healing or Repair of Tissue Damage

Alterations of wound healing and tissue damage repair are considered a potential, theoretical risk for M7824 given TGF-β role in wound healing. Management should be discussed with the Medical Monitor for participants requiring surgery on study. Post-operative wound healing will be closely monitored.

Management should be discussed with the Supporting company EMD Serono for participants requiring surgery on study.

7. DEFINITION OF DISEASE PROGRESSION/RECURRENCE

Contrast-enhanced CT of neck and chest is the first choice of imaging modality. If a participant should not receive iodinated contrast medium or due to radiation protection reasons, magnetic resonance imaging (MRI) of the same area, using gadolinium enhancement according to local protocol as permitted in conjunction with unenhanced CT of the chest from the thoracic inlet to the inferior costophrenic recess should be done. The same method should be used per participant throughout the study.

A brain CT/MRI scan should be performed, if clinically indicated by development of new specific symptoms.

Baseline scans are taken within 28 days prior to treatment. Disease must be evaluable by RECIST or RECIST 1:1. All the scans performed at baseline need to be repeated at subsequent visits for tumor assessment as per Table 1 (Summary of study evaluations). In general, lesions detected at baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

Due to the landmark end-point of progression-free survival at 1 year, this study will utilize RECIST or RECIST 1:1.

Biopsy with histopathological confirmation of first progression is required unless contra-indicated by risk to the patient.

Disease progression will be categorized as in-field or out-of-field. For the purposes of this trial, the following definitions will be utilized:

Local progression is defined as any evidence of disease progression by RECIST or RECIST 1:1 or histologically confirmed within the re-irradiation treatment field.

Regional progression is defined as any evidence of disease progression by RECIST or RECIST 1:1 or histologically confirmed 2 cm or more outside the re-irradiation field and within the head and neck or regional lymph nodes not in reirradiation field.

Distant progression is defined as any evidence of disease involving a distant organ by RECIST or RECIST 1:1 or histologically confirmed.

Due to the known phenomenon of pseudo-progression associated with SBRT, progression should be confirmed with further evaluation which may include ultrasound, FDG-PET. Biopsy for confirmation should be considered to verify disease recurrence.

8. CRITERIA FOR SUBJECT WITHDRAWAL

8.1 Withdrawal from Trial Therapy

Participants will be withdrawn from treatment for any of the following reasons:

1. Participants meeting the definition of PD while on treatment based on RECIST or RECIST 1:1 with the exception that participant may continue past PD if the ECOG PS has remained stable, and if in the opinion of the Investigator, the participant will benefit from continued treatment.

2. In case of premature withdrawal from the study treatment for reasons other than PD, the participants will be asked to attend scheduled visits, including tumor assessment and other assessments as planned until PD and end of study or death.

3. Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.

4. Therapeutic failure requiring urgent additional or alternative anticancer treatment.

5. Occurrence of AEs resulting in the permanent discontinuation of the study treatment being desired or considered necessary by the Investigator and/or the participant.

6. Occurrence of pregnancy in the participant.

7. Use of a prohibited concomitant drug, as defined in Section 9.1, where the predefined consequence is withdrawal from the study treatment if considered necessary by the Investigator or the Supporting company EMD Serono.

8. Noncompliance.

8.2 Withdrawal from Study

1. A participant may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent), and without giving a reason.

2. The participant may be withdrawn by the Investigator due to participation in another clinical study.

3. The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

4. The Schedule of Assessments specifies the data to be collected at study discontinuation and follow up, and any additional evaluations that need to be completed.

In case of withdrawal from the study:

1. The appropriate electronic case report forms (eCRFs) for the End-of-Treatment visit must be completed.

2. The day of withdrawal will correspond to the day of end of treatment and the assessments scheduled for the visit should be performed, if possible, with a focus on the most relevant assessments.

3. Participants will be asked to continue safety and survival follow up, which includes the collection of data on survival, patient reported outcome (PRO) questionnaires, and subsequent anticancer therapy. After completion of the Follow-up period or after the End of Treatment visit, whatever is applicable, the appropriate eCRF section for Study Termination must be completed.

If the participant is enrolled into a new study or any new therapy post-withdrawal from the study, the Safety Follow-up visit should be scheduled prior to the start of the new treatment irrespective of the 28-day safety follow up period.

8.3 Premature Discontinuation of the Trial

The whole study may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the study drug, for example, due to:
- evidence of inefficacy of the study drug,
- occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
- other unfavorable safety findings.

(Note: Evidence of inefficacy may arise from this study or from other studies; unfavorable safety findings may arise from clinical or nonclinical examinations, for example, toxicology.)

- Supporting company EMD Serono's decision that continuation of the study is unjustifiable for medical or ethical reasons.

- Poor enrollment of participants making completion of the study within an acceptable time frame unlikely.
- Discontinuation of development of the Supporting company EMD Serono's study drug.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

The whole study may be terminated or suspended upon request of Health Authorities.

8.4 Definition of End of Study

If the study is not terminated for a reason given in Sections 8.1, 8.2 or 8.3, the end of the study is defined as 1 year after the last participant receives the last dose of M7824.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1 Permitted Medicines/Prohibited Medicines

Permitted Medicines

Any medications (other than those excluded by the clinical study protocol) that are considered necessary for the participants' welfare and will not interfere with the study drug may be given at the Investigator's discretion.

The Investigator will record all concomitant medications taken by the participant during the study, from the date of signature of informed consent, in the appropriate section of the eCRF.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

Blood transfusions and erythroid growth factors are permitted for hemoglobin (Hgb) ≤ 7 g/dL and/or for life-threatening- bleeding.

Prohibited Medicines

As stated in the exclusion criteria, participants must not have had prior therapy with any antibody or drug targeting programmed- death 1 (anti-PD-1) or anti-PD-L1, concurrent systemic anticancer treatment, or cytokine therapy (except for erythropoietin), major surgery (excluding prior diagnostic biopsy), concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of study treatment.

In addition, the following treatments must not be administered during the study:

- Immunotherapy, immunosuppressive drugs (ie, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of immune-related adverse events [irAEs]), or other experimental pharmaceutical products. Short-term administration of systemic steroid (ie, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed. Also, hormone replacement with corticosteroids for adrenal insufficiency is allowed if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or equivalent prednisone per day.

Prophylactic use of corticosteroids for infusion-related reactions is prohibited. **However, short courses of steroids may be used at the discretion of the treating physician to prevent pain and/or swelling due to inflammation associated with SBRT, particularly transient neurogenic pain common in skull-based tumors.**

- Any vaccine therapies for the prevention of infectious disease (e.g., seasonal flu vaccine, human papilloma virus vaccine) except administration of the inactive influenza vaccine.

- If the administration of a nonpermitted concomitant drug becomes necessary during the study, the participant will be withdrawn from study treatment (the Supporting company EMD Serono may be contacted to discuss whether the study treatment must be discontinued).

Medications other than those specifically excluded in this study (see above) may be administered for the management of symptoms associated with the administration of M7824 as required. These might include analgesics, anti-nausea medications, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

9.2 Permitted/Prohibited Procedures

The following nondrug therapies must not be administered during the study (and within 28 days before the start of study treatment) before the verification of PD by the IRC:

- Major surgery (excluding prior diagnostic biopsy)

- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

Any diagnostic biopsies collected for clinical reasons during the study should be documented as a concomitant procedure including the outcome of available pathological reports.

10. ASSESSMENT OF SAFETY

Respective safety measures comprise inclusion/exclusion criteria for participation in clinical studies with M7824, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study treatment interruption or discontinuation.

10.1 General Assessments

The safety profile of M7824 will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings, including vital signs, laboratory tests, ECOG PS, and 12-lead electrocardiogram (ECG) recordings.

The AE reporting period for safety surveillance begins when the participant receives the first dose of the investigational agent and continues until last Safety Follow-up visit or before start of any anticancer therapy, whatever comes first.

The safety assessments will be performed according to the Schedule of Assessments in Table 1.

10.2 Adverse Drug Reactions Requiring Treatment Modification

Clinical Laboratory Assessments

It is essential that the Supporting company EMD Serono or designee be provided with a list of laboratory normal ranges before shipment of study drug. Any change in laboratory normal ranges during the study will additionally be forwarded to the CRO and the Supporting company EMD Serono.

All routine laboratory analyses will be performed at a laboratory facility local to the study site, and relevant results must be available and checked before administration of treatment (details to be provided in the Laboratory Manual).

If a participant has a clinically significant abnormal laboratory test value that is not present at baseline, the test should be closely monitored until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

The report of the results must be retained as a part of the participant's medical record or source documents.

Abnormal laboratory findings and other abnormal investigational findings (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (eg, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

See the Schedule of Assessments in Table 1 for further details.

Specific Planned Assessments or Adverse Events of Special Interest

AESIs are serious or non-serious AEs specific to known mechanism of action of the treatment drug that are of clinical interest requiring ongoing monitoring and rapid communication for optimal on-time management.

IRRs, including immediate hypersensitivity

Any signs or symptoms experienced by participants during the infusion or any event occurring during or within one day of drug administration should be evaluated as potential IRRs. IRRs are common ADRs with monoclonal antibodies (mAbs) timely related to drug administration and have been reported as anaphylaxis, anaphylactoid reactions and cytokine release syndrome, among other terms used. IRRs are an AESI for M7824, and important identified risks (adverse reactions) for M7824, the precautions and management are discussed in Section 0.

Immune-related adverse events (irAEs)

Immune-related AEs are defined as off target side effects associated with exposure of an immunogenic drug and are consistent with an immune mechanism. In the process of identification of irAEs, any possible etiology of neoplastic, infectious, metabolic, toxin, or any other factor should be ruled out. Serologic, histologic (biopsy), and/or immunologic results should be obtained to evaluate the differential diagnosis and/or support an immune-mediated cause. Immune-related AEs are AESIs for M7824 and important identified risks for M7824, the precautions and management are discussed in Section 0.

Skin adverse events

Skin AEs are AESIs for M7824, and include 2 potential mechanisms:

1. Skin AEs possibly due to TGF-β inhibition: rash with hyperkeratosis, KA, and SCC. Skin lesions with hyperkeratoses, keratoacanthoma, cSCC possibly due to TGF-β inhibition are identified risks for M7824. For more information, see Section 0.

Treatment-related skin lesions with hyperkeratosis, KA, cSCC possibly due to TGF-β inhibition were reclassified as important identified risks (adverse reactions) at the end of the safety reporting period of July 2017; however, they have been manageable and did not lead to permanent discontinuations in Studies EMR200647-001/EMR200647-008.

2. Immune-related skin AEs (irAEs) possibly mediated by PD-L1 inhibition (events in this category are also reported under irAEs). For more information, see Section 0.

Treatment-related anemia adverse events

Anemia is considered a potential risk based on toxicological findings with M7824 in the cynomolgus monkey indicating a decrease in Hgb, red blood cells (RBCs), and hematocrit that was fully reversible or showed a substantial trend toward recovery. Treatment-related anemia AEs are AESIs for M7824. A consistent clinical risk of treatment-related anemia on M7824 was not observed in Study EMR200647-001. As summarized in the Investigator Brochure, treatment-related anemia was reported in 6.1% (n=23)

of the participants from a number of cohorts. For more information, see Section 0 and refer to the Investigator Brochure.

Alterations in wound healing or repair of tissue damage

Due to the involvement of TGF-β in repair of skin and other tissue injuries, alterations in wound healing or repair of tissue damage is considered a potential risk. No AEs have been reported in Phase I studies. For any surgeries conducted post-treatment initiation, surgical wound healing will be closely monitored.

Embryo fetal toxicities

Embryo fetal toxicities are a known risk of the PD-1/PD-L1 targeting class. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue (Guleria, 2005; Leber 2010; Wafula, 2009; Zenclussen 2013). Embryofetal and reproductive toxicities have also been investigated in animal models for a humanized mAb targeting TGF-β1. At a dose as high as 30 mg/kg, no maternal reproductive toxicity or embryofetal lethality was observed (Hilbish 2016).

Respective safety measures comprise inclusion/exclusion criteria for participation in clinical studies with M7824, guidance for prevention, monitoring, and medical management of potential risks, as well as guidance on study treatment interruption or discontinuation.

Methods of AESI recording and reporting will follow the guideline for AE recording and reporting. Refer to the Investigator Brochure for reporting the identified risks.

Embryo fetal toxicity is an important potential risk of M7824. An appropriate contraception warning is provided as part of inclusion criteria. Pregnant and breastfeeding women are not allowed in the M7824 study and adequate contraceptive measures are recommended during the study to minimize or eliminate the potential risk to the developing fetus.

Functional and patient reported outcomes include but are not limited to:

- Validated clinical grading criteria (Head and Neck-Lymphedema and Fibrosis, HN-LEF)
- Patient-reported measures of head and neck fibrosis (Lymphedema Symptom Inventory Distress Scale, L-SIDS)[3]
- Radiographic dysphagia grade (Dynamic Imaging Grade of Swallowing Toxicity, DIGEST)
- Cervical range of motion (CROM).

Biomarker Assessments

Due to limited understanding of the biological activities induced by M7824 and radiation in cancer subjects, biomarker assessment will be conducted to examine if the doses are associated with relevant antitumor immune activities. As part of the translational work, this trial will serve to:

1. Evaluate PD-L1 expression as a predictor of response

2. Evaluate the effect on TGFβ concentrations in plasma.

3. Evaluate potential predictive / prognostic biomarker candidates related to the drug and / or the cancer (such immune infiltrating populations, tumor mutational burden, systemic cytokine profiles)

    a. Pancancer Immune Profiling Formalin-Fixed Paraffin-Embedded (FFPE) based assay using Nanostring or HTG technology.

    b. Immune infiltrating populations will be analyzed by immunohistochemistry (IHC), and Multiplex IF analyses.

        i. IHC markers will include, but are not limited to, PD-L1 (clone E1L3N, 405.9A11, 28-8, EPR1161(2), SP142, SP263, 22C3, E1J2J), CD20, CD61, LAG3, PD1, CD21, CD66b, OX40, CD3, CD3, CD68, B7-H3 (CD276), CD4, CD33, CD73, B7-H4 (VTCN1), CD5, CD38, CD137, TIM-3, CD8, CD45 LCA, FOXP3, VISTA, CD11b CD45 RO, Granzyme B, CD14, CD56, ICOS, CD19, CD57 (Leu-7), IDO-1.

        ii. Multiplex IF Analysis. Up to 10 immune markers, various panels of immune markers may be utilized. Panel #1, CD3, CD8, CD68, PD-L1, PD-1 pan-cytokeratin and DAPI; Panel #2, CD20, CD45RO, FOXP3, Granzyme B, CD57, pan-cytokeratin and DAPI. Myeloid panel 5: Arg1, Cd68, CD11B, CD33, CD14, CD66B, AE1/AE3/, DAPI. For multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. From various optimized panels, additional will be selected according the results of the gene expression analysis and may include other immunotherapy targets (e.g., OX-40, Vista, GITR, TIM-3, LAG-3, NKp46/CD16, etc.) and proliferation markers (e.g., Ki67).

        iii. RNAscope. TGF-β and other additional markers may be analyzed by RNA scope.

    c. Immune infiltrating populations and systemic cytokine profiles

        i. Blood collections and biopsies will be collected for immune studies under the supervision of the Translational Molecular Pathology Immunoprofiling Lab (TMP-IL) at MD Anderson.

        ii. Fresh tissue will be available for flow cytometry for assessment of the proportion of MDSC, macrophage, DC and NK cell subsets within the Live CD45+ cells in panel 3. The expression of checkpoint ligands will be explored using panel 4. Live cells will be sub-gated as CD45-negative to exclude immune cells. EPCAM will be used as a marker of

tumor cells and CD90 as a fibroblast marker. The expression of CD80, CD86, GITR-L, ICOS-L, MIC A/B, B7-H3, B7-H4, CD73, PD-L2, OX40L and other relevant immune cells will be assessed.

iii. In peripheral blood, evaluation by circulating immune populations will include, but not be limited to, $CD4^+$, $CD8^+$, NK, T_{reg}, monocytes and neutrophils as outlined by the Schedules of Assessments (**Tables 1**). High order flow cytometry panels will be designed. The panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ, TNFα, GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells. The proposed studies will be conducted retrospectively on cryopreserved PBMCs.

v. Serum Cytokine Analyses. Cytokines (IFN-γ, IL-1α, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, and TNF-α) will be measured in the serum using the Meso Scale Discovery Platform (Rockville, MD). This technology allows for the detection of up to 40 analytes per well and uses a very low sample volume. This method has a sensitivity up to 1000 fold higher than traditional ELISA assays with a large linear range of 3-4 logs. The instrument performs immunoassays utilizing electrochemiluminescense to detect the signal in a 96 well plate format. This technology can be utilized for either single agent detection or in multiplex format. A wide menu of validated single or multiplex kits for the detection of 1 to 40 analytes are available from the manufacturer and can be customized.

d. Mutational profiling

i. Genomic profile will be assessed via next generation sequencing in a panel of 409 genes that sequences known hotspots to a coverage of at least x250 coverage depth performed in the Molecular Diagnostic Laboratory (MDL) at MD Anderson. The lab is CAP accredited and CLIA certified to perform high complexity molecular testing for clinical purposes.

ii. TGFβ signaling pathway mutations may also be assessed via this panel which will include, but not limited to, TGFβR2, ACVR2A, SMAD2 and SMAD4.

iv. iv. Circulating free DNA (cfDNA) will be analyzed in peripheral blood using the Guardant Health platform to monitor tumor response and progression. Identified gene mutations will be correlated with target DNA sequencing in the tumor sample.

i.

b. TCR sequencing

TCR sequencing analysis may be performed using DNA from tumor tissues as well as PBMC. Briefly, 500 ng tumor DNA or 3-6 ug PBMC DNA will be subjected to high throughput TCR Vβ CDR3 sequencing on an Illumina HiSeq sequencer with at least 5-fold coverage by ImmunoSEQ™ sequencing (Adaptive Biotechnologies, Seattle, WA). TCR diversity and

clonality (defined as 1-(entropy)/log2(#) of productive unique sequences, where the entropy term takes into account the varying clone frequency) will be calculated using a software by Adaptive Technologies. T-cell repertoire diversity and clonality will be correlated with clinic-pathological parameters such as response to treatment, survival and immune infiltrating profile as well as genomic profiles (total mutation burden, non-synonymous mutation burden, predicted neoantigen burden, clonal mutation burden and clonal predicted neoantigen burden). TCR profile generated from treatment-refractory tumors at the time of disease progression will be compared to data from pre-treatment tumor samples to explore the TCR repertoire evolution of these tumors under therapeutic pressure. The dynamic changes of TCR from PBMC, when longitudinal blood samples are available, will be correlated to response to immune checkpoint blockade or chemotherapy and survival.

Details of time points and sampling are provided in the Schedules of Assessments (**Table 1**). An SOP detailing the tissue collection will be available to clinical team.

All proposed biomarker analyses are exploratory and dependent on the quality and availability of sufficient materials. The panel of biomarkers might be adjusted based on results from ongoing research related to anti-PD-1 / PD-L1 therapies and / or safety, therefore, each subject will also be asked whether any remaining tumor tissue and blood-derived samples can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug and / or disease-related aspects. A subject's consent to the use of any remaining samples for such future exploratory research shall be optional and shall not affect the subject's participation in the current trial.

11. PHARMACOKINETICS

Samples for PK and ADA will be collected according to the Schedule of Assessments in Table 1.

The following PK parameters will be estimated and reported in the PK Analysis Set:

- Ceoi
- Ctrough
- Blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of M7824, as specified in the Schedule of Assessments. Instructions for the collection and handling of biological samples will be provided by the Supporting company EMD Serono. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of M7824. Each serum sample will be divided into 2 aliquots (1 each for PK and a back up). Samples collected for analyses of M7824 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted. Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation.

Table 5 Pharmacokinetic Parameters

Symbol	Definition
C_{eoi}	The concentration observed immediately at the end of infusion
C_{trough}	The concentration observed immediately before next dosing (corresponding to pre-dose or trough concentration for multiple dosing)

PK and ADA samples collected at the same time points may be used interchangeably if the dedicated sample has insufficient quantity as the participants will have consented to all collections and tests.

PK sampling:
Prior to infusion and immediately after infusion: cycle 1, day 1 and cycle 3 day 1
Prior to infusion cycle 2 day 1 and cycle 6 day 1 OR end of treatment (whatever comes first) and follow-up visit.ADA sampling:
Prior to infusion cycle 1 day1 and cycle 6 day 1 or end of treatment (whatever comes first) and follow-up visit.

12. ADVERSE EVENTS

The investigator is required to report to the supporting company EMD Serono or its representative all AEs occurring during the clinical study (Title 21 Code of Federal Regulations [CFR] Part 312.64[b] and International Conference on Harmonization [ICH] E6 [R2]).

At each study visit, subjects will be evaluated for new Adverse Events (AE) and the status of existing AEs. All AEs observed from the date of the first administration of study treatment until the end of the follow-up period of the study (study cut-off date) are to be recorded on the AE page of the e-CRF. The date of onset and resolution, determination of seriousness, severity, grade, corrective treatment, outcome, and relationship to study treatment (M7824, Radiotherapy) will be recorded for all AEs.

All Serious Adverse Events (SAEs) occurring from the date of onset of the study treatment until the end of follow-up period of the study (study cut-off date) will be collected.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for adverse event (AE) reporting. The CTCAE version 5.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in

this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study therapy.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Serious Adverse Events (SAEs) will be reported within 24 hours of acknowledge by the study team, unless it occurs over the weekend or holidays, when it will be notified in the first business day. They are defined as any adverse drug event (experience) occurring at any dose that results in any of the following outcomes: death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Toxicities will be assessed by the treating physician/s according to the CTCv5 criteria.

Early onset (acute) toxicities occurring prior to 90 days will also be considered late onset (chronic) toxicities if they persist for at least one day beyond the 90 days used to define late onset (chronic) toxicities. In analyses that examine acute and chronic toxicities separately, those toxicities that began as acute but became chronic will be included in both the analysis of acute toxicities and in the analysis of chronic toxicities.

Immune-related AEs should be documented as an 'Adverse Event of Special Interest (AESI),' and it is recommended to involve the Medical Monitor at first incidence and subsequently as needed for follow up. Details of the diagnostic work up will be requested by the study team. Immune-related AEs are described in Section 0.

For reporting irAE severity/toxicity grading, refer to NCI-CTCAE v.5 toxicity grading system.

Toxicities related to radiation therapy include: Pain, mucositis, constipation, dysphagia, odynophagia, hemoptysis, epistasis, trismus, fatigue, weight loss, dysgeusia, nausea, radiation dermatitis, myelosuppression, skin erythema, subcutaneous fibrosis, esophagitis, myelitis, superficial soft tissue fibrosis and esophageal stricture.

Toxicities related to IO therapy are described in detail in the investigator's brochure.

Toxicity monitoring: Both Acute (From radiation start to 90 days after completion of radiation therapy) and Late (90 days to 2 years from the completion of radiation therapy) side effects of radiation therapy will be documented and graded according to the NCI-CTCAE version 5.0.

Table 6: Adverse Event Recording Guidelines

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

SAEs, whether related or not related to study drug, must be reported to EMD Serono within 24 hours. SAEs must be recorded on BMS approved form.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the EMD Serono (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The principal investigator will ensure that all SAEs in the clinical database are reported to EMD Serono and any applicable health authority during the conduct of the study.

SAEs will be reported on MDACC IRB approved form for prompt reporting (full form):

"Internal SAE Report Form for Prompt Reporting" Institutional Review Board.

SAEs will be submitted to both the Office of Protocol Research, Unit 1437 at The University of Texas MD Anderson Cancer Center and also sent to MEDWATCH

All SAEs should simultaneously be faxed or e-mailed to EMD Serono.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

Definition of Dose Limiting Toxicity (DLT)

DLT for the combination of SBRT and M7824 in patients with recurrent HNSCC will be defined as:

1. Any ≥ grade 3 AE resulting in inability to complete radiotherapy due to toxicity related to M7824 or the combination of M7824 and SBRT.

Drug destruction

Normal saline solution may be disposed of according to local site procedures. Other items used in the dose preparation and administration should be disposed of according to local site procedures.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design and Study Endpoint Summary

This protocol will be performed at M.D. Anderson, with a safety lead-in study to evaluate the safety, tolerability and feasibility of SBRT plus M7824 prior to initiation of the phase 2. The primary outcome for this study is the progression free survival (PFS) rate.

This is a phase I/II, open label, single arm study to evaluate M7824 plus SBRT in patients with locoregional recurrent HNSCC after prior head and neck therapy that are not good candidates for salvage surgery (Figure 1). Patients must have evaluabledisease by RECIST or RECIST 1:1 and a performance status ECOG 0-2. Time elapsed from prior radiotherapy must be at least 6 months.

13.2 Safety Lead-in

The Dose limiting toxicity (DLT) window for the combination of SBRT and M7824 in patients with recurrent HNSCC is from first M7824 administration (D1) until 14 days post SBRT (D28).

Patients will be administered 12 cycles of M7824 1200 mg intravenously every 2 weeks (Q2W), starting 2 weeks prior to the first fraction of SBRT until disease progression, intolerability, or consent withdrawal for up to 1 year. A cohort of 8 patients will be enrolled in the lead-in phase to assess safety and toxicity. More than 2 DLTs in 8 evaluable patients will be considered unacceptable.

With a cohort of 8 patients, the probability of the combination M7824 plus SBRT will be considered too toxic with a probability of 0.86 if the DLT rate is 50%. If the DLT rate is 0.20, the probability that the therapy will be deemed safe is 80%.

The phase 2 trial will proceed based upon the DLT data from the first 8 patients. Data from all patients will be evaluated when available.

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Bayesian toxicity monitoring will be applied to evaluate the safety profile of the treatment in the first 20 patients (including both Phase I and Phase II parts of the study). The first time of the toxicity monitoring will be in the cohort of the first 8 patients as described earlier. The treatment is considered too toxic if Probability (DLT rate > 0.3) > 0.6. Based on the criteria and a prior distribution of the probability of toxicity as beta (0.3, 0.7), the patient enrollment will be halted if the numbers of observed DLTs exceed the following stopping rules:
at least 3 in 8, 4 in 9-11, 5 in 12-14, 6 in 15-17, and 7 in 18-20 patients.

If the stopping boundary is crossed, the results will be reported to the principal investigators and the study supporting company EMD Serono. The PI and supporting company EMD Serono will review this data to determine if the study design will need to be adjusted. By applying this rule, the following table shows the operating characteristics of the Bayesian toxicity monitoring rule. The results were obtained from the Bayesian toxicity monitoring program version 2.1.1 at http://ibl.mdanderson.org/BTM/.

Scenario	Prob.Of.Tox	Prob.Early.Stop	Prob.Declare.Tox	Avg.N.Patients
1	0.1	0.045	0.045	20.444
2	0.2	0.272	0.279	17.832
3	0.3	0.611	0.631	13.986
4	0.4	0.866	0.883	10.754
5	0.5	0.973	0.979	8.948

13.3 Phase II Primary Endpoint

The study primary endpoint is progression free survival (PFS) rate at 1 year.

13.4 Secondary Endpoints

- The study secondary endpoints include: Overall response rate by RECIST or RECIST 1:1

- 1- year locoregional control (LRC), locoregional failure free survival (LFFS), distant metastasis (DM) and overall survival (OS) rates
- Acute and late toxicity accessed by the Common Terminology Criteria for Adverse Events (CTCAE)-5.0
- Fibrosis-related toxicities/functional outcomes
- Patient Reported Outcome (PRO) measures of symptoms using MD Anderson Symptom Inventory (MDASI).
- Volumetric tumor regression rate and MRI kinetic biomarkers after M7824 plus SBRT therapy
- Quality-Adjusted-Life-Years (QALY) between M7824 plus SBRT reirradiation and historic SBRT reirradiation control

13.5 Sample Size

The statistical considerations for the Phase I/II design are described as follows:

This is a phase I/II, open label, single arm study to evaluate M7824 plus SBRT in patients with locoregional recurrent HNSCC after prior head and neck radiotherapy that are not good candidates for salvage surgery (Figure 1). Patients must have evaluable disease by RECIST or RECIST 1:1 and a performance status ECOG 0-2. Time elapsed from prior radiotherapy must be at least 6 months.

Sample Size

In the phase I portion, 8 patients will be enrolled to access safety and toxicity. The primary endpoint is dose-limiting toxicity (DLT) defined as M7824 related ≥ grade 3 adverse event (AE) unresolved to ≤ grade 1 in ≤ 28 days, or incomplete SBRT. DLT window is from first M7824 dose (D0) until 14 days post SBRT (D28). More than 2 DLTs in 8 evaluable patients will be considered unacceptable.

In the phase II portion, the primary endpoint is PFS at 1 year. Based on the prior studies [unpublished data from MD Anderson], we assume that the one-year PFS of the standard treatment is 0.60. If the new treatment improves the one-year PFS to 0.80 or higher, it will be considered a clinically important improvement. A sample size of 21 patients (with 1.5-year additional follow-up after the last patient is enrolled) will allow us to observe an improvement in 1-year PFS from 0.60 to 0.80. This will enable the study 80% power to detect the specified difference in PFS. Power was calculated using a log-rank test with a one-sided type 1 error rate of 0.10 (EAST 5.4 and STPLAN version 4.5). Based on our estimated accrual rate of 2 patients per month, we expect enrollment to be completed in 11 months. The total study duration is 29 months.

DMI (Data Management Initiative) database

Clinical data capture called DMI (Data Management Initiative) and CORe will be the electronic database used for this study's electronic case report forms.

13.6 Statistical Analysis

Summary statistics including mean, standard deviation, median, and range will be provided for continuous variables such as age, BMI, lab measurements, and scores from some HR-PRO measures of symptoms, and frequency count and percentage will be provided for categorical variables such as gender, response, toxicity type and severity.

To assess the primary endpoint (PFS), we will use the methods of Gooley et al. [44] to estimate the cumulative incidence of PFS "events". A PFS event is defined as death or disease progression, including locoregional recurrence/progression or distant metastases. Time to PFS event is measured from treatment initiation until a recurrence, progression or occurrence or death, whichever occurs first.

Secondary endpoints include local-regional control, locoregional failure-free survival (LFFS), distant metastases (DM), DM free survival (DMFS) and overall survival (OS). Local failure is defined as failure (recurrence or progression) within the prescribed radiation field, including failure within 2 cm of the radiation field. Local control is defined as absence of local failure. LFFS is defined as alive and free of local recurrence or progression. Time to an LFFS event is measured from treatment initiation until local failure or death from any cause, whichever occurs first. Similarly, time to a DMFS event is measured from treatment initiation until distant metastases or death from any cause, whichever occurs first. Finally, OS is measured from treatment initiation until time to death from any cause.

The student t-test or the Wilcoxon rank sum test will be used to compare continuous variables between patient groups. The chi-square test or the Fisher's exact test will be applied to evaluate the association between two categorical variables. Logistic regression models will be used to evaluate the effects of the important patient clinical factors including treatment on PFS. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Proportional hazards regression may be employed for multivariate analysis on time-to-event outcomes. PROs will be assessed at the completion of reirradiation, and subsequently every ±3-months until 24-months post reirradiation. Generalized linear models for the repeated measures analysis will be performed to assess the change in PROs overtime with important covariates including treatment in the models.

The Investigator is responsible for completing safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval.

Lead in phase/phase I:
Toxicity summary will be submitted after the first eight evaluable patients' complete 1 cycle of therapy.

Approval from IND office will be obtained before advancing to phase 2.

Phase II:
Toxicity summary will be submitted after first 3 evaluable patients' complete 1 cycle of therapy and every 3 evaluable patients complete cycle 1 thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

13.7 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigators will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but patient confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

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