JAVELIN HEAD AND NECK 100

A RANDOMIZED DOUBLE-BLIND PHASE 3 STUDY OF AVELUMAB IN COMBINATION WITH STANDARD OF CARE CHEMORADIOTHERAPY (CISPLATIN PLUS DEFINITIVE RADIATION THERAPY) VERSUS STANDARD OF CARE CHEMORADIOTHERAPY IN THE FRONT-LINE TREATMENT OF PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Compound:	MSB0010718C
Compound Name:	Avelumab
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2016-001456-21
Protocol Number:	B9991016
Phase:	3

Document History

Document	Version Date	Summary of Changes
Amendment 3	31 Jul 2019	Major changes: • The Protocol Summary and Section 9.1 were revised to reflect the changes resulting from the update in the timing of the interim analysis from a PFS information fraction of 60% to 75%. The increase in information fraction from 60% to 75% will allow for an interim analysis with more mature data. • Section 9.1, 9.3.2.1, and 9.6 were revised to reflect the changes resulting from the increase in the number of interim analyses for OS from 3 to 4. Other changes: • Footnote 7 of the Screening, Lead-In Phase, and Definitive Treatment (Chemoradiotherapy) Phase SOA and footnote 6 of the Maintenance Phase, EOT/Withdrawal, and Short-/Long Term Follow-up Periods SOA were updated to reflect that laboratory assessments could be collected and results reviewed on Friday (up to 1 business day) prior to avelumab administration the following Monday. • CCI • Section 5.5.1, clarified that laboratory draws and assessment of results up to 1 business day prior to study drug administration is acceptable and not considered a protocol deviation. • Section 5.5.2.2, footnote 7 of the Screening, Lead-In Phase and Definitive Treatment

		(Chemoradiotherapy) Phase SOA, and footnote 6 of the Maintenance Phase, EOT/Withdrawal, and Short-/Long Term Follow-up Periods SOA were updated to allow laboratory samples collected on Friday before administration of cisplatin on the following Monday. • Section 7.5.1 language was updated to reflect that tumor tissue collected (via slides) in China were not retained and were examined for PD-L1 expression and CD8 lymphocyte infiltration by immunochemistry, tumor mutational burden and immune repertoire by TCR analysis. • CCI [redacted] • Footnotes 21 and 22 of the Screening, Lead-In Phase, and Definitive Treatment (Chemoradiotherapy) Phase SOA, footnote 18 of the Maintenance Phase, EOT/Withdrawal, and Short-/Long Term Follow-up Periods SOA were also updated. • Section 3.8 and Footnote 17 of the Screening, Lead-In Phase, and Definitive Treatment (Chemoradiotherapy) Phase SOA, footnote 15 of the Maintenance Phase, EOT/Withdrawal, and Short-/Long Term Follow-up Periods SOA were updated to clarify that PRO assessments should coincide scheduled clinic visits, do not require an additional trip to the clinic, and will be completed in the clinic. • Footnote 2 of the SOA for the Maintenance Phase, EOT/Withdrawal Visit, and Short-/Long-Term Follow-Up Periods was

		clarified to distinguish imaging and assessment requirements for patients who complete the maintenance phase and continue into the follow-up period from those patients who discontinue early from the study and refuse follow up. • Footnotes 3 and 14 of the Maintenance Phase, EOT/Withdrawal, and Short-/Long Term Follow-up Periods SOA were updated to allow for additional collections of survival information. • Section 4.1 and IC #8 updated to include the minimum age for entry for patients in Taiwan and Korea. [redacted] • Section 12.2, compliance language was updated to remove incorrect dates and versions.
Amendment 2	22 March 2018	This country specific change concerns the addition of Appendix 11 to capture some operational items not included in the mandatory contract format for France (ie, French "Contrat Unique"), which Pfizer includes in standard contract language for other countries. The items included do not impact the conduct of the trial, the safety or integrity of the subject, or use of their data. The information being added relates to requirements for: 1. GCP Training 2. Investigational Product 3. Inspections
Amendment 1	30 January 2018	Major changes: • Inclusion Criterion (IC) No. 2 was clarified to include patients with HPV-positive

		oropharyngeal disease T4 OR N2c OR N3 per TNM guidelines for head and neck sites. Section 1.2.3.4 and Section 1.3, were updated accordingly. • Inclusion Criterion (IC) No. 8 was updated to include patients with a creatinine clearance of at least 60 ml/min if this value is described in the contra-indications for cisplatin as per country's local labeling. • Inclusion Criterion (IC) No. 11 and Exclusion No 14 were updated as per the new guideline on Lifestyle, requiring the use of two methods of contraception (at least one of which is considered to be highly effective). Section 4.3 was updated to include new lifestyle guidelines. • Exclusion Criterion (IC) No. 3 was updated to exclude patients with prior malignancy requiring tumor-directed therapy within the last 2 years prior to enrollment, or concurrent malignancy associated with clinical instability. Exceptions for disease within the 2 years are specified. • CCI [redacted] • Sections 1.2.2, Avelumab clinical experience, 1.2.3.3, rationale for avelumab dose, 5.4.6.6, Table 5 and 5.4.6.9 Table 6 were updated as per Avelumab Investigator Brochure version 7. Other changes: • Section 3.1, study design was updated to include clarification for possible extension of CRT phase. The 14 days mandatory interval between two consecutive doses of avelumab/placebo was removed. • Sections 3.2 and 7.8, Tumor assessments, were

		updated to include high resolution PET/CT and clarify that baseline scans obtained within 28 days prior to randomization, are acceptable. • Section 5.4.1.4, compliance criteria, was further clarified for radiotherapy. • Section 5.4.2 cisplatin dosing, was updated to include requirement for dosing calculation based on actual weight in accordance with ASCO guidelines for obese patients. Guidance for split dose provided. • Section 5.4.3.2. Avelumab. Text was added to clarify that, for weight changes ≤10%, the decision on whether to recalculate the avelumab dose will be made in accordance with local practices. • Section 5.5.1.4, special precautions for avelumab/placebo, was updated to include new guidance for required premedication and for observation post infusion (30 min). • Section 5.5.1 text was clarified to better define the beginning of maintenance and allowed 3 days visit window except for C1D1. • Section 5.5.1.5, management of avelumab/placebo infusion related reactions, updated to include guidance for infusion rate reduction. • Sections 5.5.2.2.1 and section 5.5.2.3, updated to allow administration of the 3rd cisplatin infusion any time up to 5 days after the end of radiation therapy. • Section 5.5.2.2.2, cisplatin related ototoxicity, updated to include audiogram requirements in accordance with country specific label. • Section 5.8, concomitant treatments, updated to include reporting period of up to 90 days after last dose of study treatment or until the start of a new

		therapy, whichever comes first. • Section 5.8.2, Hematopoietic Growth Factors, updated to clarify that the use of erythropoietin is prohibited during radiation therapy and that CSF administration for the management of treatment-emergent neutropenia requires consultation and approval from sponsor. • The Schedule of Activities (SoA), Table 2 for Screening/Lead-in phase and CRT phase assessments and table 3 for maintenance/ EOT/withdrawal visit/ follow up periods assessments, were updated to include relevant changes and clarifications and specify the requirement that laboratory assessments must be performed and results reviewed by the treating physician prior to study drug administration. HPV status (P16) assessed prior to screening is allowed and baseline nasopharyngoscopy is strongly recommended. • Appendix 8, appropriate chemotherapy dosing for obese adults with cancer as per ASCO guidelines added, clarifying BSA calculation. [redacted] • Typos and inconsistencies were corrected; references and abbreviation list were updated.
Original protocol	20 Jun 2016	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background

Head and neck cancers, including cancers of the oral cavity, nasopharynx, pharynx, and larynx, account for approximately 5% of cancers worldwide (excluding non-melanoma skin cancers).[9] Approximately 680,000 new cases of head and neck cancer were diagnosed in 2012 with 370,000 deaths attributed to this disease; of these new cases reported, almost 140,000 were in Europe, and over 90% were squamous cell histology.[10] In the US, it is estimated that over 61,000 people will be diagnosed with head and neck cancer in 2016 and over 13,000 will die from this cancer.[62] Head and neck cancers are predominately squamous carcinomas. Squamous cell carcinomas of the head and neck (SCCHN) involving the oral cavity, larynx, oropharynx, and hypopharynx account for 75% SCCHN overall and are closely associated with alcohol and tobacco use. SCCHN of the oropharynx is also closely associated with human papillomavirus (HPV) type 16 infection.[11] In the past 2 decades, HPV-positive oropharyngeal cancers have increased dramatically especially in North America, underscoring an important role in HPV infection and oropharyngeal cancer.[12] Although the incidence of HPV-negative SCCHN has decreased, consistent with decreasing use of tobacco products worldwide, the curability of HPV-negative tumors remains suboptimal.[43]

Of newly diagnosed patients with SCCHN, approximately 60% present with locally or regionally advanced disease.[10,13] Depending on the tumor site, stage, and resectability, locoregional failure rates can range between 35% and 65%. With a median PFS of 1.9 years and reported 3-year PFS rate of 61.2%, this disease will ultimately recur locally in a large proportion of treated patients, with distant metastases developing in 10% to 30% of these patients.[13,44,57] Currently available treatment options for both locoregional and distant recurrences are limited. Outcomes for both groups of recurrences are abysmal, and the limited number of patients who are eligible for potentially curative treatment for locoregional disease recurrence are exposed to a high degree of morbidity.

Study Rationale

There are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[18,19] Chemotherapy has been shown to have immunostimulatory properties by stimulating the release of neoantigens and adjuvants by dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells.[20,21,22,23]

Several immune checkpoint inhibitors have been combined with chemotherapy agents. The addition of ipilimumab to dacarbazine led to an improvement in PFS and OS in previously untreated melanoma compared to dacarbazine alone.[25] Ipilimumab was combined with platinum doublet chemotherapy in small cell as well as non-small cell lung cancer (NSCLC) with encouraging results.[26,27] Single-arm studies investigating the combination of programmed death protein 1 (PD-1) blockers (pembrolizumab, nivolumab) as well as a programmed death-ligand 1 (PD-L1) blocker (atezolizumab) with platinum doublet chemotherapy demonstrated acceptable safety profiles with early evidence of clinical activity

which appears to be higher than expected for platinum doublet therapy alone, particularly for atezolizumab.[27,28,29,30,31] Randomized Phase 3 studies in the first-line treatment of NSCLC patients are currently investigating the addition of pembrolizumab and atezolizumab to platinum-based chemotherapy.

In addition to the data supporting combining immune checkpoint inhibitors with chemotherapy, a strong body of evidence supports the combination of radiation therapy with immunotherapy such as a PD-L1 inhibitor.[34,35] Radiation therapy (RT) in combination with avelumab was found to be highly synergistic, capable of causing complete regression of established tumors with the potential to generate antitumor immune memory.[17]

There are currently several studies ongoing evaluating immune checkpoint inhibitor agents in later lines of treatment for SCCHN patients. These trials have demonstrated activity in this tumor type for this class of drugs when used as single agents for patients with recurrent or metastatic disease. Nivolumab, in the CheckMate – 141 study in platinum-refractory patients in the recurrent or metastatic setting, has demonstrated an improved OS relative to alternative investigator-choice chemotherapy at 7.5 (95% confidence interval [CI]: 5.5 – 9.1) vs. 5.1 (95% CI: 4.0 – 6.0) months (HR 0.70 [97.73% CI: 0.51 – 0.96]), and was stopped early by the data monitoring committee (DMC). Updates presented at the American Society of Clinical Oncology (ASCO) 2016 Annual Meeting described the activity in subgroups of patients with tumors that were p16 positive (N=63 HR 0.56, 95% CI: 0.32 - 0.99) or negative (N=50, HR 0.73, 95% CI: 0.42 - 1.25) and those whose tumors were positive for PD-L1 staining at ≥1% (HR: 055; 95%CI: 0.36-0.83) vs. ≤1% (HR: 0.89 95% CI: 0.54-1.45).[59] Also at ASCO, updated efficacy data for pembrolizumab in recurrent/metastatic SCCHN (KEYNOTE-012) was presented. An overall objective response rate (ORR) of 18% (34/192; 95% CI: 13-24%) was observed, with ORR of 24% (11/45, 95% CI: 13 - 40%) and 16% (23/147, 95% CI: 10 – 23%) in HPV-positive and HPV-negative patients, respectively. However, the limited number of patients evaluated and overlapping 95% CIs preclude definitive conclusions regarding any role HPV or PD-L1 status may play in response to checkpoint inhibitor treatments. Additionally, it should be noted that both HPV groups had the same (n=4) number of patients with CR in the KEYNOTE-12 update. Median time to response was 2 months, but several patients took substantially longer to respond (range: 2 - 17 months). Median OS was 8 months (95% CI: 6 – 10 months) in these heavily pretreated patients with 38% alive at 12 months.[60,61] These trials provide strong early evidence that SCCHN represents a tumor type that is responsive to this class of agents. Collectively, these data, the strong scientific rationale for radiation (which increases PDL-1 expression) and immune checkpoint inhibitor combinations, and the poor patient options if disease control is not obtained in front-line therapy, persuasively argue for progressing an immune checkpoint inhibiting agent into combination therapy with definitive chemoradiotherapy (CRT) to provide an optimized, multimodality approach to treat this disease and help patients avoid the high morbidity and mortality associated with disease progression. This combination can potentially overcome the treatment resistance that patients experience, in particular for HPV-negative tumors.[43]

Study Objectives and Endpoints

Primary Objective

To demonstrate that treatment with avelumab in combination with standard of care (SOC) CRT is superior to SOC CRT alone in prolonging progression-free survival (PFS) in front-line patients with high-risk (as defined in Inclusion Criterion 2 [Section 4.1]), locally advanced SCCHN who are candidates for definitive CRT with cisplatin.

Secondary Objectives

- To compare the overall survival (OS) of avelumab in combination with SOC CRT vs SOC CRT alone.
- To evaluate the anti-tumor activity of avelumab in combination with SOC CRT and SOC CRT alone.
- To evaluate the overall safety and tolerability profile of avelumab in combination with SOC CRT and SOC CRT alone.
- To evaluate the pharmacokinetics (PK) of avelumab.
- To evaluate the PK of cisplatin (total and free).
- To assess avelumab anti-drug antibodies (ADAs).
- To evaluate the effect of avelumab in combination with SOC CRT and SOC CRT alone on patient-reported outcomes (PROs) of disease-related symptoms and health-related quality of life.
- To evaluate candidate immune-related predictive biomarkers of sensitivity or insensitivity to treatment with avelumab in combination with SOC CRT in pre-treatment tumor samples (eg, PD-L1 expression).
- To evaluate candidate immune-related predictive biomarkers of sensitivity or insensitivity to treatment with avelumab in combination with SOC CRT in tumor samples (eg, PD-L1 expression) after one dose of avelumab in patients who provide this optional biopsy.

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Primary Endpoint

- PFS per modified Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 (see Appendix 3 for specific modifications, including pathologic confirmation) by investigator assessment.

Secondary Endpoints

- OS.
- *Antitumor Activity:* Pathologic complete response in any resected specimens, neck dissection.
- *Antitumor Activity:* Locoregional failure, objective response, distant metastatic failure, and duration of response, per modified RECIST v1.1 (Appendix 3) by investigator assessment.
- *Safety:* Adverse events and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; vital signs (blood pressure, pulse rate).
- *Pharmacokinetics:*
  - Maximum concentrations (C_{max}) and trough concentrations (C_{trough}) for avelumab.
  - Area under the concentration-time curve extrapolated to infinity (AUC_{inf}), C_{max}, clearance (CL), time to maximum plasma concentration (T_{max}), elimination half-life ($t_{1/2}$), and volume of distribution (V_z) for cisplatin (total and free), as data permit.
- *Immunogenicity:* Incidence of ADA (neutralizing antibody) against avelumab.
- *Patient-Reported Outcomes:* Disease-related symptoms and Health-Related Quality of Life as measured by the National Cancer Comprehensive Network (NCCN) Head and Neck Symptom Index-22 items (FHNSI-22), and the EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L).
- *Biomarkers:* Tumor tissue biomarkers including, but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T-lymphocytes.

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- [redacted]
- [redacted]

Study Design

This is a Phase 3, international, multicenter, randomized, double-blind, parallel, 2-arm study in patients with previously untreated, histologically confirmed, locally advanced SCCHN (oral cavity, oropharynx, larynx, or hypopharynx) who are candidates for definitive CRT with cisplatin. The study is designed with the primary objective of demonstrating that treatment with avelumab in combination with SOC CRT is superior to SOC CRT alone in prolonging PFS.

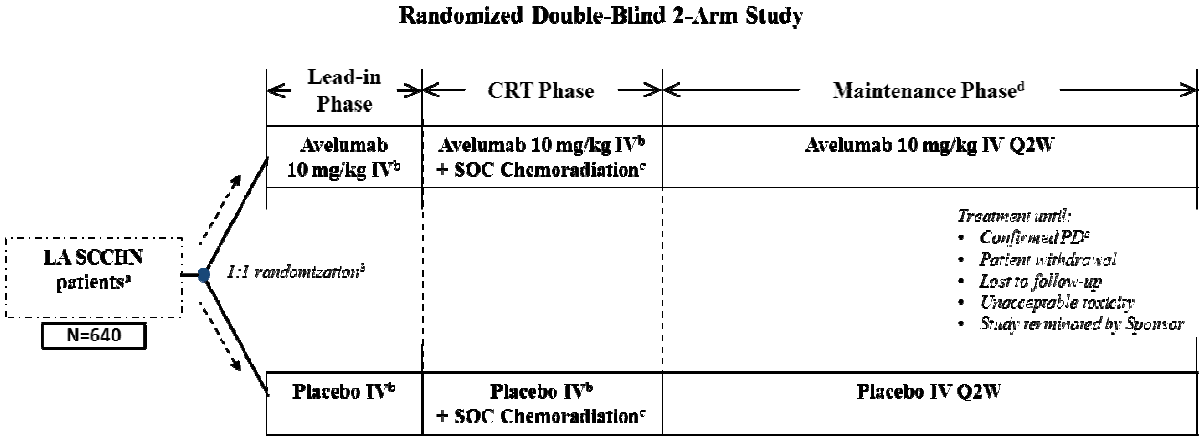
One interim analysis for the assessment of PFS will be conducted to allow early stopping of the study for futility or to demonstrate early superiority of avelumab in combination with SOC CRT compared to SOC CRT alone, and to assess the safety of avelumab in combination with SOC CRT.

A total of approximately 640 patients will be randomized in a 1:1 ratio to either Arm A (avelumab + SOC CRT) or Arm B (placebo + SOC CRT). Randomization will be stratified by tumor (T) stage (<T4 vs T4), nodal (N) stage (N0/N1/N2a/N2b vs N2c/N3), and HPV status (positive vs negative) as measured by p16 expression by IHC.

The specific study treatments to be administered in each treatment arm are described in the STUDY TREATMENTS section below.

The study design is illustrated in Figure 1.

Figure 1 Study Design



a. Patients with LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx) eligible for front-line treatment: HPV negative disease stage III, IVa, IVb; non-oropharyngeal HPV positive disease stage III, IVa, IVb; HPV positive oropharyngeal disease T4 OR N2cOR N3 (staging per TNM [tumor, node, metastases] guidelines for head and neck sites AJCC 7th Edition). (Note: entry criteria for patients with HPV-positive tumors are different than for patients with HPV-negative tumors).

b. Avelumab or placebo IV to be administered on Day 1 of the Lead-in Phase (1 week prior to the start of the CRT Phase) and on Days 8, 25, and 39 during the CRT Phase.

c. SOC CRT = IMRT (70 Gy/35 fractions/7 weeks; 1 fraction per day, 5 fractions/week) for 7 weeks + cisplatin (100 mg/m^2 Days 1, 22, 43) during the CRT Phase.

d. Maintenance Phase to start after completion of the CRT Phase and continue for 12 months.

e. Patients will continue treatment until confirmed disease progression as assessed by Investigator per modified RECIST v1.1.

AJCC = American Joint Committee on Cancer; CRT = chemoradiotherapy; HPV = human papillomavirus; IMRT = intensity-modulated radiation therapy; LA = locally advanced; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SCCHN = squamous cell carcinoma of the head and neck; SOC = standard of care.

There will be 3 treatment phases in this study:

- Lead-in Phase: On Day 1 of the Lead-in Phase of the study, patients will receive a single dose of avelumab or matching placebo, administered 7 days prior to initiation of the CRT Phase;

- CRT Phase: Avelumab or matching placebo will be administered on Days 8, 25, and 39 in conjunction with SOC CRT starting on Day 1 of the CRT phase;

- Maintenance Phase: Following completion of the CRT Phase, avelumab or matching placebo will be administered every 2 weeks (Q2W) for 12 months during the Maintenance Phase.

The treatment schedule is described in the following table.

Table 1. Chemoradiation and Avelumab/Placebo Treatment Schedule

	Lead-in Phase (7 days)[a]	CRT Phase (63 days)									Maintenance Phase[b]
	-- Day --	---------- Day ----------									
	1	1	8	15	22	25	29	36	39	43	
IMRT (70 Gy/35 fractions/ 7 weeks; 1 fraction per day, 5 fractions/week [Monday – Friday])		X→	X→	X→	X	→	X→	X→	→	X→	
Cisplatin (100 mg/m^2 Q3W)		X			X					X	
Avelumab (10 mg/kg) or placebo	X		X			X[c]			X		Q2W

a. Lead-in Phase to start 7 days prior to initiation of CRT Phase.
b. Maintenance Phase to start after completion of the CRT Phase (ie, 2 weeks following completion of CRT) and be 12 months in duration. CRT phase may be extended as required for patient recovery from CRT; however, it is hypothesized that patients will receive maximal benefit from beginning maintenance as close to the scheduled time as possible.
c. Day 25 dose of avelumab/placebo during the CRT Phase may be administered between Day 24 and Day 29.

Cisplatin should be administered on a Monday or Tuesday to maximize overlap with IMRT.

CRT = Chemoradiotherapy; IMRT = intensity-modulated radiation therapy; Q2W = every 2 weeks; Q3W = every 3 weeks.

Tumor Assessments

- Tumor assessments will be completed on the schedule detailed below using a modification of RECIST v1.1. The modification is required in head and neck cancer assessment as these tumors are fairly unique in their accessibility for thorough clinical evaluation and biopsy. Furthermore, the extensive mucosal surface which is available for clinical evaluation of tumor response or recurrence may indicate tumor status changes that may not be present or as clear on radiographic imaging alone. Conversely, radiographic changes that could be suggestive of tumor progression or recurrence can reflect radiation therapy changes. Taken collectively, this has given rise to the clinical practice of using biopsies to directly assess tumor recurrence in this patient population. Therefore, RECIST was modified for this protocol to recognize this practice and better confirm (through direct pathologic ascertainment) when tumor recurrence has occurred.

- Radiographic and clinical evaluations will be conducted with the same schedule in both treatment arms of the study. The investigator will assess antitumor activity based on radiological assessments and clinical evaluation of patients using modified RECIST v1.1 (see Appendix 3) at baseline, 12 weeks after the completion of CRT, every 16 weeks (Q16W) thereafter for 48 months (208 weeks), and every 24 weeks (Q24W) thereafter until confirmed disease progression per modified RECIST v1.1

and regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy.

- Radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or physical exam findings suggestive of mucosal recurrence).

- Locoregional disease progression per modified RECIST v1.1 requires that radiographic changes suggestive of disease progression are confirmed by biopsy. Pathologic confirmation of progression will verify that radiographic changes represent true tumor progression and not radiation effects or non-malignant contrast enhancement.

- When disease progression occurs for distant metastases per RECIST v1.1, confirmation of pathology is recommended unless medically contraindicated or if the lesion location is too high risk for biopsy.

- If a patient withdraws from study treatment for a reason other than disease progression per modified RECIST v1.1, radiological tumor assessments are to continue until disease progression per modified RECIST v1.1, even if a new anti-cancer therapy is initiated.

- A head and neck computed tomography (CT) or magnetic resonance imaging (MRI), chest CT, and PET scan are required at baseline and at 12 weeks after the completion of CRT. High resolution PET/CT does not require additional CT thorax/neck/brain. MRI brain may be performed if clinically indicated. Subsequent PET scans may be performed during the Maintenance Phase in the absence of clinical or CT complete resolution of nodal disease (described in Section 3.3) or at the investigator's discretion.

Surgical Salvage of Residual Disease after Completion of the CRT Phase

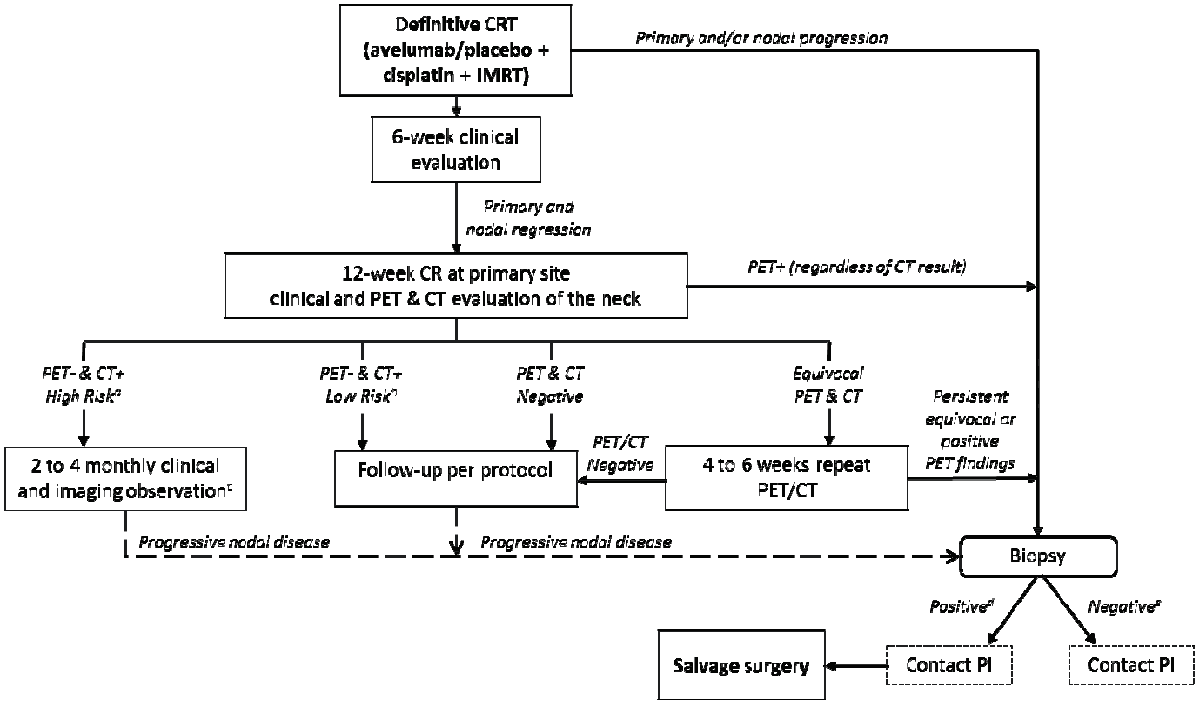
Treatment of residual disease at the primary site will be determined by the investigator and the clinical situation (see Figure 2). If treatment at the primary site is necessary after completion of CRT, study treatment has failed and the patient will discontinue treatment. Surgical resection, re-irradiation, chemotherapy, or palliative care may be performed per institutional policy. If the primary site is cleared of residual disease, yet residual disease at the cervical nodal basin is suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling of the node is negative. Residual disease in the neck is not considered treatment failure if surgical salvage is completed within 140 days of completion of CRT. A primary treatment neck dissection after completion of the CRT Phase will be defined as a neck dissection performed for residual disease and within 20 weeks (140 days) after completion of CRT. Patients who undergo such a primary treatment neck dissection will remain on study treatment.

Positive neck specimens removed within 140 days of completion of CRT will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures. Such consolidation neck dissections after completion of the CRT Phase will encompass only the areas (typically only levels 2 and 3) initially involved in the side of the neck in question. The extent of neck dissections performed for nodal recurrence, nodal progression, and/or salvage of disease at the primary will be determined by the treating surgeon.

If a neck dissection is required, then the treating surgeon is required to contact the surgical Principal Investigator (PI) of this study, Dr. PPD prior to the surgery to discuss the clinical and radiologic findings as well as the planned surgery itself. Notes from the surgery, as well as the pathology report from the neck dissection, must also be submitted to Dr. PPD for review when they become available, but no later than 6 weeks following the procedure.

In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal complete response (CR) at the tumor assessment performed 12 weeks following completion of CRT, follow-up PET scans are recommended every 4 months (Q16W) with the CT imaging for 24 months (104 weeks), then every 6 months (Q24W) in Years 3-5, as well as careful recording of the clinical dimensions of the residual abnormality. CT imaging should be obtained as described in the Schedule of Activities beyond Year 5.

Figure 2 Algorithm for Evaluation of Regional Lymph Nodes Following Definitive CRT



a. High risk = perceived risk of residual disease is high, such as sub-optimally treated patients due to premature cessation of treatment, unplanned treatment interruptions.
b. Low risk = perceived risk of residual nodal disease is low, such as low burden disease without treatment interruption.
c. Ongoing clinical and imaging observation until residuum is <1 to 1.5 cm or stable for >6 months.
d. In the case of positive biopsy, the surgical PI (Dr. PPD]) must be contacted prior to performing the surgery to discuss the clinical and radiological findings as well as the planned surgery itself.
e. If biopsy is negative but there is high clinical/radiologic suspicion of disease, consider rebiopsy and contact the surgical PI (Dr. PPD]) for discussion.

CRT = chemoradiotherapy; CT = computed tomography; IMRT = intensity-modulated radiation therapy; PET = positron emission tomography; PI = (surgical) principal investigator.

Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as described in the Schedule of Activities table.

Pharmacokinetic/Immunogenicity Assessments

Samples for PK and immunogenicity analyses will be collected as described in the Schedule of Activities table.

Biomarker Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and SOC CRT. In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action, as well as potential mechanisms of resistance, to the combination of avelumab with SOC CRT. Tumor and blood biospecimens as required for the various analyses will be collected as described in the Schedule of Activities table.

Study Treatments

- Arm A: Avelumab + SOC CRT:
  - Avelumab 10 mg/kg intravenously (IV): Day 1 of the Lead-in Phase; Days 8, 25, and 39 of the CRT Phase; and Q2W for 12 months during the Maintenance Phase.
  - Cisplatin 100 mg/m^2 IV: Days 1, 22, and 43 of the CRT Phase.
  - Intensity Modulated Radiation Therapy (IMRT) 70 Gy/35 fractions/7 weeks; 1 fraction per day, 5 fractions/week for 7 weeks during the CRT Phase.
- Arm B: Placebo + SOC CRT:
  - Placebo IV matching avelumab: Days 1 of the Lead-in Phase; Days 8, 25, and 39 of the CRT Phase; Q2W for 12 months during the Maintenance Phase.
  - Cisplatin 100 mg/m^2 IV: Days 1, 22, and 43 of the CRT Phase.
  - IMRT 70 Gy/35 fractions/7 weeks; 1 fraction per day, 5 fractions/week for 7 weeks during the CRT Phase.

Statistical Methods:

The primary endpoint of the study is PFS per modified RECIST v1.1 by investigator assessment. PFS is defined as the time from the date of randomization to the date of the first documentation of objective progressive disease (PD) per modified RECIST v1.1 or death due to any cause, whichever occurs first.

Two hundred eighty-nine (289) PFS events will be required to have at least 90% power to detect a hazard ratio of 0.68 using a 1-sided log-rank test at a significance level of 0.025, and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-7) β-spending function to determine the non-binding futility boundary.

The sample size of 640 patients for this study is determined based on the assumptions that the median PFS for patients in Arm B is 33 months[43,44] and that combination treatment including avelumab (Arm A) is expected to increase the median PFS to ≥48.5 months, corresponding to a hazard ratio (HR) of ≤0.68 under the exponential model assumption. The sample size further assumes a 15% drop-out rate within each treatment arm and a non-uniform patient accrual over a 22-month period. The data cutoff date for the primary PFS analysis will occur after the target number of events has been reached and the last patient randomized in the study has been followed for at least 24 months after randomization.

The primary analysis of PFS will include all patients who are randomized. A stratified log-rank test (1-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses with the overall significance level preserved at 0.025 (1-sided). PFS times associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th, and 75th percentiles will be reported. The stratified Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CIs.

For the primary analysis, PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD per modified RECIST v1.1 or death); the analysis will consider any PD per modified RECIST v1.1 or death as an event regardless of the number of prior missing tumor assessments or timing of the event with respect to initiation of anti-cancer therapy.

A sensitivity analysis for PFS will be performed using the methodology outlined for the primary analysis of PFS above but defining PD as per standard RECIST v1.1. Summary of discordance of PD (event and timing) as well as reasons for discordance between assessment of PFS per modified RECIST v1.1 and standard RECIST v1.1 will be provided for each treatment arm.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

If deemed clinically necessary, the investigator may schedule visits in addition to those listed in the Schedule of Activities table (unplanned visits) at any time to conduct evaluations or assessments required to protect the well-being of the patient.

Table 2. SCHEDULE OF ACTIVITIES – Screening, Lead-in Phase, and Definitive Treatment (Chemoradiotherapy) Phase

Visit Identifiers[1]	-- Screening --	---------- Study Treatment ----------									
Protocol Activities		Lead-in Phase	Chemoradiotherapy (CRT) Phase ([±2] days for each visit)								
	≤28 Days Prior to Randomization[18]	Day 1 (7 days prior to initiation of CRT Phase)	------ Day ------								
			1	8	15	22	25	29	36	39	43	50 - 63*
Clinical Assessments												
Informed Consent[2]	X											
Medical/Oncological History	X											
Baseline Signs/Symptoms[3]		X										
Physical Examination[4]	X	X		X			X			X		
Contraception Check[5]	X	X		X			X			X		
ECOG Performance Status	X	X		X			X			X		
Vital Signs[6]	X	X	X	X		X	X			X	X	
Laboratory Studies												
Hematology[7]	X	X	X	X		X	X			X	X	
Blood Chemistry[7,8]	X	X[8]	X[8]	X[8]		X[8]	X[8]			X[8]	X[8]	
Coagulation[7]	X	X	If clinically indicated									
Thyroid Function and ACTH Tests[9]	X											
Pregnancy Test[10]	X	X	X	X		X	X			X	X	
Urinalysis[11]	X		If clinically indicated									
HBV, HCV Tests	X		If clinically indicated									
12-Lead ECG[12]	X	X	if clinically indicated									
Disease Assessments												
HPV status (measured by p16 status)[13]	X											
Tumor Assessments (including scans)[14]	X											

Table 2. SCHEDULE OF ACTIVITIES – Screening, Lead-in Phase, and Definitive Treatment (Chemoradiotherapy) Phase

Visit Identifiers[1]	-- Screening --	---------- Study Treatment ----------										
Protocol Activities		Lead-in Phase	Chemoradiotherapy (CRT) Phase ([±2] days for each visit)									
	≤28 Days Prior to Randomization[18]	Day 1 (7 days prior to initiation of CRT Phase)	------ Day ------									
			1	8	15	22	25	29	36	39	43	50 - 63*
Other Clinical Assessments												
Adverse Events[15]		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications/Treatments[16]	X	X	X	X	X	X	X	X	X	X	X	X
Patient-Reported Outcomes (NCCN-FHNSI-22, EQ-5D-5L, CCI)[17] CCI		X	X					X				
Randomization and Study Treatment[18]												
IMRT (70 Gy/35 fractions/ 7 weeks; 1 fraction per day,5 fractions/week			X→	X→	X→	X→	→	X→	X→	→	X→	
Cisplatin (100 mg/m^2 Q3W)[18]			X			X					X	
Avelumab or Placebo Q2W[18]		X		X			X			X		
Other Samplings												
Avelumab Pharmacokinetics[19]		X		X			X					
Cisplatin Pharmacokinetics[20]			X									
Banked Blood Biospecimens[21]		X	X	X	X							
Mandatory Tumor Tissue[22]	X											
Optional De Novo Biopsy[23]		X										
Anti-Avelumab Antibodies and Neutralizing Antibodies[24]		X		X			X					

* A 2-week observation period will follow completion of CRT therapy.
ACTH = adrenocorticotropic hormone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded HBV = hepatitis B virus; HCV = hepatitis C virus; HPV = human papillomavirus; CCI CCI PK = pharmacokinetics; Q2W = every 2 weeks, Q3W = every 3 weeks; Q12W = every 12 weeks.

Footnotes for Schedule of Activities FOR SCREENING, LEAD-IN PHASE AND CRT PHASE
1. **Visit Identifiers:** All assessments should be performed prior to dosing with study treatments unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers where applicable.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure.
3. **Baseline Signs/Symptoms:** To be recorded pre-dose on Day 1 of the Lead-in Phase. Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization. Baseline signs and symptoms should be recorded in the medical history case report form (CRF) page.
4. **Physical Examination:** Includes an examination of major body systems including height (screening only), and weight and whole nasopharyngeal area. (nasopharyngoscopy strongly recommended).
5. **Contraception Check:** Patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 contraception methods (at least one of which is considered to be highly effective as defined in Section 4.3) consistently and correctly and document such conversation in the patient's chart. The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient.
6. **Vital Signs:** vital signs to include blood pressure and pulse rate. Blood pressure and pulse rate should be taken before any other assessments (eg, PK, laboratory blood draws), prior to receipt of study treatment with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
7. **Hematology, Blood Chemistry (full panel), and Coagulation:** Results from the Screening assessments may be used for Day 1 of the Lead-in Phase if they were performed within 7 days prior to the visit. All assessments may also be performed when clinically indicated. Full chemistry panel is required at screening only. Laboratory assessments may be performed and results reviewed by the treating physician up to 1 business day prior to study drug administration.
8. **Blood Chemistry (core panel):** Core chemistry panel is required on Day 1 of the Lead-in Phase; and Days 1, 8, 22, 25, 39, and 43 of the CRT Phase. Core panel must be performed, and results reviewed by the treating physician prior to study drug administration. When an infusion is shifted towards another day, chemistry panel will be shifted accordingly; additional assessments whenever clinically indicated.
9. **Thyroid Function and ACTH Tests:** Free T4, TSH, and ACTH tests will be performed at Screening and every 8 weeks thereafter. Additional tests should be performed when clinically indicated.
10. **Serum/Urine Pregnancy Test:** For patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study treatment: once at the start of screening and once on the Day 1 of the Lead-in Phase immediately before avelumab/placebo administration. Additional pregnancy tests (serum or urine) will also be routinely repeated prior to avelumab/placebo dosing during the CRT Phase and Maintenance Phases. In addition, pregnancy tests will be performed whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations. Results of the pregnancy test should be evaluable prior to each dosing.
11. **Urinalysis:** Required only at Screening. To be performed as clinically indicated at other time points.

12. **12-Lead Electrocardiogram (ECG):** All patients require a single ECG measurement at screening. Triplicate ECGs will be collected in at least 30 patients in each treatment arm. In these patients, on-treatment triplicate ECGs will be performed on the day of avelumab/placebo administration (ie, Day 1 of the Lead-in Phase, and Days 8, 25, and 39 of the CRT Phase; if the avelumab/placebo dosing day is shifted for patient scheduling reasons, the ECG assessment should be shifted also). At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates) prior to avelumab/placebo administration and at the end of infusion. Additional single ECGs may be performed as clinically indicated. Clinically significant findings seen on ECGs during the treatment period should be recorded as adverse events.
13. **HPV status** will be determined per institutional standard using p16 immunohistochemistry (IHC). HPV status (p16) assessed prior to screening window is allowed for study.
14. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging at screening (baseline) and at 12 weeks following completion of CRT must include a head and neck computed tomography [CT] or magnetic resonance imaging [MRI], chest CT, and Positron Emission Tomography (PET) scan. High resolution PET/CT does not require additional CT thorax/neck/brain. MRI brain may be performed if clinically indicated. Other areas may be scanned as clinically indicated. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique(s) used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. At minimum, the CT modality used at baseline will be the expected imaging technique for follow-up. Any clinical progression concern warranting a biopsy must have supporting imaging (ie, CT, MRI, PET, or digital photograph) archived for documentation purposes. Additional imaging modalities may also be employed if clinically required. Radiographic and clinical evaluations will be conducted with the same schedule in both treatment arms of the study. The investigator will assess antitumor activity based on radiological assessments and clinical evaluation of patients using modified RECIST v1.1 at baseline, 12 weeks after the completion of CRT, every 16 weeks thereafter for 48 months (208 weeks), and every 24 weeks thereafter until confirmed disease progression per modified RECIST v1.1 and regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy. Radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or physical exam findings suggestive of mucosal recurrence). The assessment performed 12 weeks after completion of the CRT is to include CT and PET for all patients and MRI also if clinically appropriate to delineate the extent of the local tumor. Subsequent scans are to include CT of the head and neck and thorax. In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal CR at the tumor assessment performed 12 weeks following completion of CRT, follow-up PET scans are recommended every 4 months (16 weeks) with the CT imaging for 24 months (104 weeks), then every 6 months (24 weeks) in Years 3-5. CT imaging should be obtained as described herein beyond Year 5. All radiographic images will be collected and stored for possible future objective verification by an independent third-party core imaging laboratory (central review) as described in the Study Manual. Photographs of clinical progression will also be collected for potential future review. Baseline tumor assessments should be done within 28 days prior to randomization.
15. **Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor. AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has initiated any study treatment through and including 90 calendar days after the last administration of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

16. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded for all patients from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment or until the start of new therapy, whichever comes first. All concomitant medications and non-drug supportive interventions should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis, infusion reaction prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

17. **Patient-Reported Outcomes:** All scheduled assessments of the NCCN FHNSI-22, EQ-5D-5L, CCI must be completed in the clinic by the patient prior to any other study or medical procedures - these cannot be taken home. PRO assessments should be conducted during scheduled clinic visits (Q16W through 48 months) and do not require additional clinic visits. Subsequent PRO assessments will be Q24W until PD. CCI

18. **Randomization:** An interactive voice and web response system (IVRS) will be used for randomization to a treatment arm. Required information: site and patient identifiers, and demographic information. Patients meeting all entry criteria will be randomized and will be administered the first dose of study treatment preferably on the day of randomization, but no later than 3 days after randomization.
    Study Treatment:
    Arm A: Avelumab + SOC CRT
    Arm B: Placebo + SOC CRT
    In both treatment arms, study treatment will be initiated with a Lead-in avelumab/placebo Phase followed by a Chemoradiotherapy (CRT) Phase and a Maintenance Phase. In both arms, BSA must be calculated prior to each cisplatin administration and patient must be weighed prior to each avelumab/placebo administration. Specific therapies to be administered include the following:
    - Lead-in Phase: avelumab 10 mg/kg (Arm A) or placebo (Arm B) administered on Day 1 (7 days prior to the start of the CRT phase).
    - CRT Phase: avelumab 10 mg/kg (Arm A) or placebo (Arm B) administered on Days 8, 25, and 39 in combination with cisplatin 100 mg/m^2 on Days 1, 22, and 43 plus intensity modulated-radiation therapy (IMRT) 70 Gy/35 fractions/7 weeks; 1 fraction/day, 5 fractions/week. **Cisplatin should be administered on a Monday or Tuesday if feasible to maximize overlap with IMRT**. The Day 43 dose of cisplatin can be given any time up to 5 days after the end of radiation therapy.
    - Maintenance Phase: avelumab 10 mg/kg (Arm A) or placebo (Arm B) administered Q2W for 12 months. The Maintenance Phase starts following completion of CRT Phase (ie, 2 weeks following completion of CRT).

    Patient weight should be verified prior to dose calculation for each of the study treatments.
    See Section 5.5.1.5 and 5.5.2.1 for mandatory premedications to be administered with avelumab/placebo and cisplatin, respectively.

19. **Avelumab Pharmacokinetics:** Blood samples (3.5 mL) for avelumab PK will be collected in all patients: pre-dose (within 2 hours before the start of avelumab/placebo infusion) and at the end of infusion (immediately before until 10 minutes after the end of avelumab/placebo infusion) on Days 1 of the Lead-in Phase and Days 8, and 25 of the CRT Phase.

20. **Cisplatin Pharmacokinetics:** Blood Samples (5 ml) for cisplatin PK (total and free) will be collected in a total of 24 patients (12 patients in Arm A and 12 patients in Arm B) at selected sites at pre-dose, mid-infusion, end of infusion (immediately before the end of cisplatin infusion), and 3, 4, and 24 hours post start of cisplatin infusion on Day 1 of the CRT Phase.

21.	CCI [redacted] CCI [redacted]
22.	**Mandatory Tumor Tissue:** An archival formalin fixed, paraffin embedded (FFPE) tumor tissue block from the most recent tumor resection or biopsy must be provided for all patients enrolled in the study and submitted to the Central Laboratory prior to randomization. If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. Tumor tissue collected in China (via slides) will not be retained and will be examined for PD-L1 expression and CD8 lymphocyte infiltration by immunochemistry, tumor mutational burden, and immune repertoire by TCR analysis.
23.	**Optional De Novo Tumor Biopsy – Lead-in Phase:** An optional tumor biopsy, to be collected 4 to 7 days following the single dose of avelumab in the Lead-in Phase, is requested for analysis of potential biomarkers of response. The de novo biopsy should be FFPE per routine (see Study Manual), and the resulting tissue block(s) submitted to the central laboratory.
24.	**Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL at each time point) for ADA will be collected at pre-dose on Day 1 of the Lead-in Phase, and Days 8, and 25 of the CRT Phase. All samples should be drawn within 2 hours before the start of avelumab or placebo infusion. All samples that are positive for ADA may also undergo characterization for Nab.

Table 3. SCHEDULE OF ACTIVITIES – Maintenance Phase, End of Treatment/Withdrawal, and Short-/Long-Term Follow-up Periods

Visit Identifiers[1]	-- Study Treatment --		---------- Post-Treatment ----------			
Protocol Activities	**Maintenance Phase* (1 cycle = 4 weeks)**		**End of Treatment (EOT)/ Withdrawal (+3 days)[2]**	**Follow-up[3]**		
	Day 1 (±3 days)	**Day 15 (±3 days)**		**Short-Term (after last dose or EOT/Withdrawal Visit)**		**Long-Term (+ 14 days)**
				30 days (±3 days)	**90 days Follow-up Telephone Contact* (±3 days)**	
Documentation						
Physical Examination[4]	X		X			
Contraception Check	X		X	X		
ECOG Performance Status	X		X	X		
Vital Signs[5]	X	X	X			
Laboratory Studies						
Hematology & Blood Chemistry[6]	X	X	X	X		
Coagulation[6]	If clinically indicated		X	If clinically indicated		
Thyroid Function Tests and ACTH[7]	X (then Q8W)		X	X		
Pregnancy Test[8]	X	X	X	X		
Urinalysis[9]	If clinically indicated		X	If clinically indicated		
12-lead ECG[10]	If clinically indicated		X			
Disease Assessments						
Tumor Assessments (including scans)[11]	X (12 weeks after completion of CRT, then Q16W for 48 months, then Q24W until PD per modified RECIST v1.1; additional assessment to be performed at the EOT/Withdrawal Visit)					
Other Clinical Assessments						
Adverse Events[12]	X	X	X	X		
Concomitant Medications/Treatments[13]	X	X	X	X		
Initiation of New Systemic Anticancer Treatment			X	X	X	X
Survival Assessment[14]						X

Table 3. SCHEDULE OF ACTIVITIES – Maintenance Phase, End of Treatment/Withdrawal, and Short-/Long-Term Follow-up Periods

Visit Identifiers[1]	-- Study Treatment --		---------- Post-Treatment ----------			
Protocol Activities	**Maintenance Phase* (1 cycle = 4 weeks)**		**End of Treatment (EOT)/ Withdrawal (+3 days)[2]**	**Follow-up[3]**		
	Day 1 (±3 days)	**Day 15 (±3 days)**		**Short-Term (after last dose or EOT/Withdrawal Visit)**		**Long-Term (+ 14 days)**
				30 days (±3 days)	**90 days Follow-up Telephone Contact* (±3 days)**	
Patient-Reported Outcomes NCCN FHNSI-22, EQ-5D-5L, [redacted], and [redacted][5]	X (Day 1 Cycle 1 and Day 1 Cycle 3 of the Maintenance Phase, then Q16W for 48 months, then Q24W until PD per modified RECIST v1.1; additional assessment to be performed at the EOT/Withdrawal Visit)					
Study Treatments						
Avelumab or Placebo[16]	X	X				
Other Samplings						
Avelumab Pharmacokinetics[17]	X		X	X		
Banked Blood Biospecimens[18]		X (Cycle 1 Day 15 only)	X			
De Novo Tumor Biopsy[19]	X		X			
Anti Avelumab Antibodies and Neutralizing Antibodies[20]	X		X	X		

ACTH = adrenocorticotropic hormone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded HBV = hepatitis B virus; HCV = hepatitis C virus; HPV = human papillomavirus; [redacted], [redacted] PK = pharmacokinetics; Q2W = every 2 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; Q24W = every 24 weeks.

*** Maintenance Phase:** Maintenance Phase to start following completion of the CRT Phase and to be 12 months in duration. Study assessment window of ±3 days starting from C1D15. CRT phase may be extended as required for patient recovery from CRT; however, it is hypothesized that patients will receive maximal benefit from beginning maintenance as close to the scheduled time as possible.

Footnotes for Schedule of Activities FOR MAINTENANCE PHASE, END OF TREATMENT/WITHDRAWAL, AND SHORT-/LONG-TERM FOLLOW-UP PERIODS
1. **Visit Identifiers:** Acceptable time windows for performing each assessment are described in the column headers.
2. **End of Treatment/Withdrawal:** Visit to be performed within 3 days following the last dose of study treatment received. Obtain these assessments if not completed within 7 days prior to the EoT/Withdrawal visit, except for tumor assessments and patient-reported outcome questionnaire assessments, which need not be repeated if they have been performed within the prior 6 and 4 weeks, respectively. Patients who complete the maintenance phase and proceed to follow up will follow the prespecified timelines described in the table above. EoT/Early withdrawal imaging (if more than 6 weeks ago) and questionnaire assessments (if more than 4 weeks ago) relate only to patients who discontinue early, and refuse follow up.
3. **Short- and Long-Term Follow-up:** All patients will be followed for safety with evaluations at 30 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. The Day 90 Short-Term Follow-up Visit will be conducted as a phone call. If any concern arises, the patient will be called in for a follow-up visit within 5 calendar days for appropriate assessments (as per the investigator's medical judgement). Beyond the Day 90 Short-Term Follow-up Visit, all patients will be followed every 16 weeks (Q16W) for survival (additional survival follow up information may be requested) and new systemic anticancer treatment within the long-term follow-up period. Patients who refuse to return to the site for evaluations should be contacted by telephone as an alternative.
4. **Physical Examination:** Includes an examination of major body systems and weight.
5. **Vital Signs:** Vital signs to include blood pressure and pulse rate. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
6. **Hematology, Blood Chemistry, and Coagulation**: Hematology and core blood chemistry to be performed prior to each administration of avelumab/placebo, and at the EOT/Withdrawal and 30-day Short Term Follow-Up visits. Coagulation to be performed when clinically indicated. Full chemistry panel is required at End of Treatment/Withdrawal. All laboratory assessments may be performed and results reviewed by the treating physician up to 1 business day prior to study drug administration.
7. **Thyroid Function Tests:** Free T4, TSH, and ACTH will be performed on Day 1 and then every 8 weeks thereafter during the Maintenance Phase, and at the End of Treatment/Withdrawal and 30-day Short Term Follow-up visits after the last administration of study treatment unless performed in the prior 8 weeks.
8. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed prior to each avelumab/placebo administration during the Maintenance Phase, and at the End of Treatment/Withdrawal and 30-day Short Term Follow-up visits, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations.
9. **Urinalysis:** Required only at the End Of Treatment/Withdrawal. To be performed as clinically indicated at other time points.
10. **12-Lead Electrocardiogram (ECG):** Additional single ECG measurements may be performed as clinically indicated. For End of Treatment/Withdrawal, a single ECG measurement will be obtained for all patients. Clinically significant findings seen on ECGs should be recorded as adverse events.

11. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique(s) used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. At minimum, the CT modality used at baseline will be the expected imaging technique for follow-up. Additional imaging modalities may also be employed if clinically required. Radiographic and clinical evaluations will be conducted with the same schedule in both treatment arms of the study. The investigator will assess antitumor activity based on radiological assessments and clinical evaluation of patients using modified RECIST v1.1 12 weeks after the completion of CRT, every 16 weeks thereafter for 48 months (208 weeks), and every 24 weeks thereafter until confirmed disease progression per modified RECIST v1.1 and regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy. Radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or physical exam findings suggestive of mucosal recurrence). The assessment performed 12 weeks after completion of the CRT is to include CT and PET for all patients and MRI also if clinically appropriate to delineate the extent of the local tumor. Subsequent scans are to include CT of the head and neck and thorax. In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal CR at the tumor assessment performed 12 weeks following completion of CRT, follow-up PET scans are recommended every 4 months (16 weeks) with the CT imaging for 24 months (104 weeks), then every 6 months (24 weeks) in Years 3-5. CT imaging should be obtained as described herein beyond Year 5. The time window for tumor assessments is ±1 week except for the assessment at week 12 which cannot be done earlier but up to one week later.
12. **Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor. AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least 1 dose of study treatment through and including 90 calendar days after the last administration of the study treatment. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.
13. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded for all patients from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment or until the start of new therapy, whichever comes first. All concomitant medications and non-drug supportive interventions should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis, infusion reactions prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
14. **Survival Assessment:** All patients will be followed for survival and subsequent anticancer therapies every 16 weeks until death, end of the study, or patient withdrawal of consent, whichever comes first. For patients refusing to return to the site, a telephone follow-up call is acceptable. Additional survival information may be requested in preparation for interim and final analyses.
15. **Patient-Reported Outcomes:** All scheduled assessments of the NCCN FHNSI-22, EQ-5D-5L, CCI [redacted] must be completed in the clinic by the patient prior to any other study or medical procedures - these cannot be taken home. PRO assessments should be conducted during scheduled clinic visits (Q16W through 48 months) and do not require additional clinic visits. Subsequent PRO assessments will be Q24W until PD. CCI [redacted]

16. **Study Treatment**:
    Arm A: Avelumab + SOC CRT
    Arm B: Placebo + SOC CRT
    - Maintenance phase: avelumab 10 mg/kg (Arm A) or placebo (Arm B) administered Q2W for 12 months. The Maintenance Phase starts following completion of CRT Phase.

    Patient weight should be verified prior to dose calculation for each of the study treatments.
    During the Maintenance Phase, avelumab/placebo may be administered up to 3 days before or after the scheduled treatment day of each cycle for administrative reasons, except for C1D1. Maintenance C1D1 is defined as the day when the first avelumab/placebo is given; therefore there is no window required as it defines the beginning of maintenance whenever the infusion is given.
17. **Avelumab Pharmacokinetics:** Blood samples (3.5 mL) for avelumab PK will be collected in all patients: pre-dose (within 2 hours before the start of avelumab/placebo infusion) and at the end of infusion (immediately before the end until 10 minutes after avelumab/placebo infusion) on Day 1 of Cycles 1 and 2 of the Maintenance Phase. Thereafter, a pre-dose sample will be taken every 3 cycles (eg, Cycles, 5, 8, 11) while a patient remains on treatment. A single sample will be taken at both EOT and 30 days post-EOT.
18. CCI [redacted]
19. ***De Novo* Tumor Biopsy:** A *de novo* (ie, fresh biopsy) tumor sample should also be collected at the End of Treatment/Withdrawal visit, unless clinically contraindicated or no tumor remains. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including formalin fixed, paraffin embedded [FFPE] cell pellet material), is not adequate and should not be submitted. The *de novo* biopsy should be formalin-fixed and paraffin-embedded as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. For patients who, during the course of the study, undergo a clinically-indicate tumor resection procedure, a tumor sample from the procedure should be collected and submitted to the Central Laboratory. The tumor sample obtained during the Maintenance Phase should be FFPE as per routine (see Study Manual) and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory.
20. **Anti-Avelumab ADAs and Nab:** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected at on Day 1 of Cycles 1 and 2 of the Maintenance Phase. All samples should be drawn within 2 hours before the start of avelumab or placebo infusion. Thereafter a pre-dose sample will be taken every 3 cycles (eg, Cycles 5, 8, 11) while a patient remains on treatment. A single sample will be taken at both EOT and 30 days post-EOT. All samples that are positive for ADA may also undergo characterization for Nab.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Avelumab[1] (also referred to as MSB0010718C) is a fully human immunoglobulin (Ig) G1 antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors programmed death 1 (PD-1) and B7-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of a cytotoxic T-cell response. In addition, avelumab may mediate antibody-dependent cell-mediated cytotoxicity (ADCC) in certain settings via engagement of activating FcRs on cytotoxic natural killer cells and macrophages.

Radiation therapy is a core treatment modality in cancer therapeutics. Ionizing radiation causes cell death through the generation of free oxygen radicals, DNA double strand breaks and resulting mitotic catastrophe. The tumor is targeted, and normal tissue relatively spared through physical means including imaging based target identification and the use of intensity modulated radiation therapy that enable radiation treatment planning to limit normal tissue dosing. Cisplatin is added to the definitive radiation therapy in the treatment of head and neck cancers as a radiation sensitizing agent and has proven effective at improving OS, by, on average, 6.5% at 5 years.[36]

The dominant mode of action of cisplatin appears to be inhibition of the incorporation of deoxyribonucleic acid (DNA) precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.[37]

The mechanism of action of avelumab is further described in Section 1.2.2.

The indication under study is the front-line therapy of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN, oral cavity, oropharynx, larynx, or hypopharynx) who are eligible for definitive chemoradiotherapy (CRT) with cisplatin.

1.2. Background and Rationale

1.2.1. Head and Neck Cancer

Head and neck cancers, including cancers of the oral cavity, nasopharynx, pharynx, and larynx, account for approximately 5% of cancers worldwide (excluding non-melanoma skin cancers).[9] Approximately 680,000 new cases of head and neck cancer were diagnosed in 2012 with 370,000 deaths attributed to this disease; of these new cases reported, almost 140,000 were in Europe, and over 90% were squamous cell histology.[10] In the US, it is estimated that over 61,000 people will be diagnosed with head and neck cancer in 2016 and over 13,000 will die from this cancer.[62] Head and neck cancers are predominately squamous

[1] Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C)

carcinomas. SCCHN involving the oral cavity, larynx, oropharynx, and hypopharynx account for 75% SCCHN overall and are closely associated with alcohol and tobacco use. SCCHN of the oropharynx is also closely associated with HPV type 16 infection.[11] In the past 2 decades, HPV-positive oropharyngeal cancers have increased dramatically especially in North America, underscoring an important role in HPV infection and oropharyngeal cancer.[12] Although the incidence of HPV-negative SCCHN has decreased, consistent with decreasing use of tobacco products worldwide, the curability of HPV-negative tumors remains suboptiomal.[43]

Of newly-diagnosed patients with SCCHN, approximately 60% present with locally or regionally advanced disease.[10,13] Combination modality therapy is generally employed for these patients and may include surgery with adjuvant radiotherapy for early stage disease and/or concurrent CRT which is standard for more advanced disease.[10,14] The most widely used standard regimen used in this setting consists of 100 mg/m^2 cisplatin administered every 3 weeks (Q3W), combined with ~70 Gy radiation delivered in 1.8-2.0 Gy daily fractions. Although associated with increased local control rates and overall survival (OS) compared to radiotherapy alone, this combination is also associated with increased toxicity. Additionally, depending on the tumor site, stage, and resectability, locoregional failure rates can range between 35% and 65%.[10,13] With a median PFS of 1.9 years and reported 3-year PFS rate of 61.2%, this disease will ultimately recur locally in a large proportion of treated patients, with distant metastases developing in 10% to 30% of these patients.[13,44,57] Currently available treatment options for both locoregional and distant recurrences are limited. Outcomes for both groups of recurrences are abysmal, and the limited number of patients who are eligible for potentially curative treatment for locoregional disease, are exposed to a high degree of morbidity.

Treatment options for patients with recurrent SCCHN are limited to palliative chemotherapy and, in patients suitable for more aggressive treatment, combination systemic chemotherapy regimens.[10] Response rates to single-agent chemotherapy range from 15% to 35%, with a median OS of 6 months. With combination therapy, response rates vary from 26% to 36% with a median OS of 10.1 months. Recently presented data on single agent PD-1 blockage in the cisplatin refractory group (progression within 6 months of prior cisplatin therapy) is encouraging relative to chemotherapy, but median OS is still only 7.5 months.[55] Thus, the primary treatment of the presenting SCCHN is critical for both the prevention of highly morbid secondary local therapy and the prevention of metastatic disease. There remains an unmet medical need for improved therapy for high–risk locally advanced SCCHN.

1.2.2. Avelumab Clinical Experience

Avelumab (MSB0010718C) is a fully human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype.

PD-L1 is expressed by a variety of human tumors, both by the tumor cells, as well as by the immune cells that are present in the tumor microenvironment.[1] High levels of PD-L1 expression have been found to be associated with disease progression, increased metastases, poor response to treatment, and decreased survival in a number of human cancers.[1] Importantly, anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of

murine tumor models as monotherapy and has shown synergistic effect in the combination therapy setting.[2,3,4,5,6,7,8]

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[15,16]

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in a wide variety of adult cancers, such as non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, urothelial cancer, and Hodgkin's Lymphoma, as single agent or in combination with chemotherapy, tyrosine kinase inhibitors, or other immune-modulating agents.

The safety profile of avelumab administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in Merkel cell carcinoma (N=88). Study EMR100070-001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor types.

As of 09 June 2016, a total of 53 patients were treated in the dose escalation phase of the EMR100070-001 study, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg Q2W, respectively. None of the patients treated with doses up to 10 mg/kg experienced a dose limiting toxicity (DLT), and the 10 mg/kg dose of avelumab was thus considered a safe and well tolerated dose for further investigation in the dose expansion cohorts. One DLT (a Grade 3 immune related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

The dose expansion phase of study EMR100070-001 included patients with non-small cell lung cancer, gastric cancer, breast cancer, colorectal cancer, castration resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Study EMR100070-003 Part A was conducted in patients with Merkel cell carcinoma.

A summary of pooled safety data from patients treated at 10 mg/kg Q2W in studies EMR100070-001 and EMR100070-003 (N=1738) is provided here.

Treatment-emergent adverse events (TEAEs) were observed in 1697 (97.6%) patients, with the most frequent (≥10%) being fatigue (32.4%), nausea (25.1%), diarrhea (18.9%), constipation (18.4%), decreased appetite (18.4%), infusion related reaction (17.1%), weight decreased (16.6%), vomiting (16.2%), anemia (14.9%), abdominal pain (14.4%), cough (13.8%), pyrexia (13.6%), dyspnea (13.2%), edema peripheral (11.9%), back pain (11.8%), and arthralgia (10.4%).

Treatment-related TEAEs were observed in 1164 (67.0%) patients, and the most frequent (≥5%) were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

A total of 177 patients (10.2%) experienced Grade ≥3 treatment-related TEAEs, and the most frequent (≥0.5%) were fatigue (1.0%), lipase increased (1.0%), gamma glutamyltransferase (GGT) increased (0.6%), infusion related reaction (0.6%), and aspartate aminotransferase (AST) increased (0.5%).

A total of 777 (44.7%) patients had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 108 (6.2%) patients, with the most frequent (≥0.2%) being infusion related reaction (0.9%), pneumonitis (0.6%), pyrexia (0.3%), adrenal insufficiency (0.3%), and hypothyroidism, diarrhea, vomiting, autoimmune disorder, autoimmune hepatitis, transaminases increased, dyspnea, and colitis (0.2% each).

There were 911 deaths (52.4%) in the pooled safety data set. The majority of deaths were due to progressive disease (744, 42.8%). There were 59 (3.4%) deaths attributed to TEAEs not related to trial treatment, and 4 deaths (0.2%) attributed to a treatment-related TEAE by the investigator and which occurred up to 30 days after the last dose of avelumab: pneumonitis (1 case), acute liver failure (1 case), respiratory distress (in the context of sepsis) (1 case), and autoimmune hepatitis with hepatic failure (1 case). In addition, 1 patient died with acute respiratory failure (in the context of lung cancer progression) considered related to avelumab by the investigator 37 days after the last dose of avelumab. The cause of death was marked as "other" or "unknown" in 17 (1.0%) and 83 (4.8%) of cases, respectively.

A total of 244 patients (14.0%) permanently discontinued avelumab treatment due to TEAEs, including 107 patients (6.2%) discontinuing because of treatment-related TEAEs. The most frequent treatment related TEAEs leading to treatment discontinuation were infusion related reaction (1.8%), GGT increased (0.4%), and diarrhea, fatigue, autoimmune disorder, alanine aminotransferase (ALT) increased, blood creatinine phosphokinase (CPK) increased, lipase increased, arthralgia, and pneumonitis (0.2% each).

Immune-related adverse events (irAEs): in the pooled safety data (N=1738), a total of 247 patients (14.2%) experienced irAEs, defined as adverse events requiring use of corticosteroids (and/or hormonal therapy for endocrinopathies), and no clear alternate etiology. The median time to first onset of an irAE was 11.7 weeks. The most frequent irAEs were thyroid disorders including hypothyroidism (5.2%), hyperthyroidism (0.4%) and thyroiditis (0.2%), immune-related rash (5.2%), immune-related colitis (1.5%), immune-related pneumonitis (1.2%), immune-related hepatitis (0.9%), adrenal insufficiency (0.5%) and immune-related myositis (0.5%). In addition, irAEs reported in 0.1% of patients in the pooled safety dataset included: type 1 diabetes mellitus, immune-related nephritis/renal dysfunction, hypopituitarism, uveitis and Guillain-Barre Syndrome. The majority of irAEs were Grade 1 or Grade 2 in severity, with 39 (2.2%) being of Grade ≥3 severity. Fatal outcome was reported in 1 patient (0.1%) with immune-related pneumonitis, and 2 patients (0.1%) with immune-related hepatitis. Other relevant irAEs reported with avelumab outside

the pooled safety dataset included 1 case of fatal immune-related myocarditis in Study B9991002 (avelumab in combination with axitinib for renal cell carcinoma (RCC)), 1 case of non-fatal immune-related myocarditis in the 20 mg/kg cohort of the dose escalation phase of Study EMR100070-001, and 2 patients with non-fatal graft versus host disease (GVHD) in Study B9991007 (avelumab in patients with classical Hodgkin's lymphoma).

Infusion-related reactions (IRRs): a total of 439 patients (25.3%) experienced at least 1 IRR, defined as a TEAE coded under the PTs of infusion related reaction, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, and abdominal pain according to a predefined case definition. The most common PTs that met the definition for an IRR included: infusion related reaction (17.0%), chills (5.4%), and pyrexia (3.6%). Most of the events were of Grade 1 or Grade 2 severity. Grade ≥3 IRRs occurred in 12 patients (0.7%) including 3 patients (0.2%) who experienced Grade 4 IRRs. No Grade 5 IRRs were reported. In most cases, the first occurrence of an IRR was related to the first infusion, with only 6 patients experiencing the first IRR at the fifth or later infusion. All Grade ≥3 IRRs occurred with the first (7 patients) or second (5 patients) infusion. Overall, 21.6% of patients had 1 IRR, 2.6% of patients had 2 IRRs, 14 patients (0.8%) had 3 IRRs, and 3 patients had >3 IRRs. IRR recurrence after the fourth infusion was rare (15 patients) and all recurrent IRRs were of Grade 1 or 2 severity. In 35 patients (2.0%), treatment was permanently discontinued because of an IRR.

As required per protocol, the first eDMC review occurred after 30 patients had been randomized, treated, and followed for at least 12 weeks. At the time of the data cutoff a total of 78 patients had been randomized and 77 had received at least one dose of study treatment. The eDMC reviewed unblinded data. The Sponsor does not have access to unblinded data/data summarized by treatment arm. The eDMC recommended that the study proceed after reviewing unblinded safety data. The DMC had no requests for changes to the protocol or study conduct.

Of the 78 patients randomized in the study, 75 patients (96.2%) had entered the CRT phase, 49 (62.8%) finished cisplatin treatment phase and 26 (33.3%) were ongoing. Amongst the 72 patients who started cisplatin the median number of cisplatin infusions received was 2 (range: 1.0-3.0).

Patients that came off of protocol therapy during the CRT phase all completed SOC CRT off protocol, with the exception of a single patient who, for personal reasons, elected to stop all therapy against medical advice. For the patients who completed IMRT, the median total dose of IMRT was the protocol expected dose of 70 Gy (range: 40.0-70.0) (the individual who had 40 Gy on study completed IMRT to 70 Gy off of study). Overall AE profile was consistent with the known AE profile of CRT.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the avelumab investigator's brochure.

1.2.2.1. Clinical Experience in Patients with Carcinomas Treated with Platinum-Based Chemotherapy

Avelumab is being evaluated in patients with SCCHN in a tumor-specific expansion cohort of study EMR100070-001. In this expansion cohort, 93 recurrent or metastatic SCCHN patients, who have received ≥1 line of platinum-based chemotherapy, or are ineligible for platinum-based treatment, have received at least 1 dose of avelumab.

The overall safety profile among the 93 patients enrolled in the SCCHN cohort of Study EMR100070-001 was comparable to the safety profile described above.

In the SCCHN cohort, TEAEs were reported in 78.5% of patients and treatment-related TEAEs were reported in 44.1%. Four Grade ≥3 treatment-related TEAEs were reported in 3 (3.2%) patients and included one event each of dyspnea, vomiting, diarrhea, and hypophosphatemia. There were no Grade 5 events in the SCCHN cohort.

Immune-mediated TEAE assessed as related to avelumab by the investigators were reported in 3 (3.2%) patients and included hypothyroidism in 2 patients and hyperthyroidism in 1 patient. IRR were reported at a lower rate in the SCCHN cohort (8.6%) compared to the pooled expansion cohort (16.2%). There were no Grade ≥3 infusion-related reactions reported in the SCCHN cohort. The overall rate of TEAEs leading to treatment discontinuation in the SCCHN was 5.4% compared to 13.5% in the pooled expansion cohort and there were no TEAEs leading to treatment discontinuation that were assessed by the investigators as related to avelumab.

For the SCCHN expansion cohort, the efficacy data are still immature; however, as of 9 September 2015 for the 22 patients with at least 13 weeks of follow-up from start of avelumab treatment, the response rate (including unconfirmed partial response [PR]) was 18.2% (4/22 patients).

For the NSCLC expansion cohort, 6 months after start of avelumab treatment of the last patient in this expansion cohort (15 January 2015), the response rate (including confirmed and unconfirmed complete response [CR] and PR) was 14.1% (26/184 patients). The median progression-free survival (PFS) for the NSCLC cohort was 11.6 weeks (95% CI: 8.4 to 13.7 weeks). The median OS was 8.4 months.

For the ovarian cancer expansion cohort, 13 weeks (13 February 2015) after start of avelumab treatment of the last patient included in the interim analysis of this expansion cohort, the response rate (including confirmed and unconfirmed CR and PR) was 10.7% (8/75 patients). The median PFS for the ovarian cancer cohort was 11.4 weeks (95% CI: 6.3 to 12.0 weeks).

In summary, preliminary data from the ongoing EMR100070-001 study in SCCHN patients who have received ≥1 line of platinum-based chemotherapy or who were platinum ineligible demonstrate that avelumab has antitumor activity in SCCHN. Further, avelumab has also shown antitumor activity in NSCLC and ovarian cancer in patients who had disease progression after prior platinum-based therapy.

1.2.2.2. Pharmacokinetics of Avelumab in Humans

Avelumab pharmacokinetics and dose proportionality following the first 1-hour infusion have been characterized in 77 Caucasian patients treated in the dose escalation and expansion cohorts of Trial EMR100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of maximum concentration (C_{max}) and area under the concentration-time curve to the end of the dosing period (AUC_{τ}) increased in a dose proportionate fashion for the 10 and 20 mg/kg doses. The half-life of avelumab tended to increase with dose, likely due to target mediated disposition at lower doses (1 and 3 mg/kg), but terminal half-life of 10 mg/kg (102 ± 28 hours) and 20 mg/kg (120 ± 42 hours) doses were similar, taking into account the PK variability. This likely indicates target mediated elimination does not increase at these two doses and target occupancy is very high.

Target occupancy on peripheral blood CD3+ T-cells was investigated in human blood in vitro by flow cytometry after spiking of whole blood samples from 8 healthy volunteers with avelumab over a concentration range of 0.003-10 µg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 µg/mL ± 0.042 µg/mL with a plateau indicating at least 95% receptor occupancy reached in all blood samples at 1 µg/mL.

Pharmacokinetic profiles obtained during the dose escalation phase of Trial EMR100070-001 were utilized to investigate whether this concentration of at least 1 µg/mL was achieved throughout the dosing interval. The median ± standard deviation trough concentration (C_{trough}) at the end of the first cycle after administration of the 10 mg/kg dose is 21 ± 12 µg/mL (n=283). This median C_{trough} increases during the subsequent cycles to 25 ± 16 µg/mL (second cycle) (n=269), 27 ± 17 µg/mL (third cycle) (n=202), and remains between 27 and 36 µg/mL during the subsequent cycles (n=55–171).

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab Investigator's Brochure (IB).[17]

1.2.3. Study Rationale

1.2.3.1. Rationale for Combining Avelumab with Chemoradiotherapy

There are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[18,19] Chemotherapy has been shown to have immunostimulatory properties by stimulating the release of neoantigens and adjuvants by dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells.[20,21,22,23] Certain chemotherapy agents including platinum-based agents are mutagenic.[24] Therefore, treatment with chemotherapy may create a pro-immunogenic, hypermutated state that may be optimal for activity of immune checkpoint inhibitors. In preclinical studies, the combination of avelumab with chemotherapy (gemcitabine, oxaliplatin, 5-fluorouracil) showed improved anti-tumor activity over single-agent chemotherapy.[17]

Several immune checkpoint inhibitors have been combined with chemotherapy agents. The addition of ipilimumab to dacarbazine led to an improvement in PFS and OS in previously untreated melanoma compared to dacarbazine alone.[25] Ipilimumab was combined with

platinum doublet chemotherapy in small cell as well as NSCLC with encouraging results.[26,27] Single-arm studies investigating the combination of PD-1 blockers (pembrolizumab, nivolumab) as well as a PD-L1 blocker (atezolizumab) with platinum doublet chemotherapy demonstrated acceptable safety profiles with early evidence of clinical activity which appears to be higher than expected for platinum doublet therapy alone, particularly for atezolizumab.[27,28,29,30,31] Randomized Phase 3 studies in the first-line treatment of NSCLC patients are currently investigating the addition of pembrolizumab and atezolizumab to platinum-based chemotherapy.

There is also emerging evidence indicating that the response to chemotherapy is partly dependent on an immunological reaction against tumor cell death during treatment with chemotherapy.[32,33] Some chemotherapy agents have been shown to mediate "immunogenic" cancer cell death by activation of the immune system via release of high-mobility- group box 1 (HMGB1) and subsequent immune cell activation. These data suggest that there may also be a therapeutic interaction between chemotherapy and avelumab that may provide additional clinical benefit to that anticipated between radiation therapy (RT) and avelumab, as discussed below.

In addition to the data supporting combining immune checkpoint inhibitors with chemotherapy, a strong body of evidence supports the combination of RT with immunotherapy such as a PD-L1 inhibitor.[34,35] Radiation alone can modify the immune response in several ways to allow for synergistic effects when combined with immunotherapy, including 1) enhancement of major histocomopatibility complex (MHC) class I surface expression, calreticulin expression, and release of HMGB1; 2) enhancement of Fas cell surface receptor (FAS) surface expression; 3) activation of dendritic cells and enhancement of cross-presentation of tumor antigens; 4) increased density of tumor-infiltrating lymphocytes; and 5) the modulation of immune checkpoint molecule expression.[35] When combined with checkpoint blockade immunotherapies such as anti-cytotoxic T-lymphocyte associated protein (CTLA-4) and anti-PD-L1, improved local and systemic disease control was observed in several preclinical studies. Additionally, treatment with low doses of fractionated radiotherapy was demonstrated to lead to the upregulation of PD-L1 expression on tumor cells secondary to CD8+ T-cell production of intereferon (IFN)-γ and inhibit the antitumor response. Concomitant administration of an anti-PD-L1 mAb resulted in enhanced efficacy of radiotherapy in several mouse models of melanoma, colorectal, and breast cancer.[35] In particular, RT in combination with avelumab was found to be highly synergistic, capable of causing complete regression of established tumors with the potential to generate antitumor immune memory.[17]

There are currently several studies ongoing evaluating immune checkpoint inhibitor agents in later lines of treatment for SCCHN patients. These trials have demonstrated activity in this tumor type for this class of drugs when used as single agents for patients with recurrent or metastatic disease. Nivolumab, in the CheckMate-141 study in platinum-refractory patients in the recurrent or metastatic setting, has demonstrated an improved OS relative to alternative investigator-choice chemotherapy at 7.5 (95% confidence interval [CI]: 5.5 – 9.1) vs 5.1 (95% CI: 4.0 – 6.0) months (HR 0.70, 97.73% CI: 0.51 – 0.96) and was stopped early by the data monitoring committee (DMC). Updates presented at the ASCO 2016 Annual Meeting described the activity in subgroups of patients with tumors that were p16 positive (N=63 HR

0.56, 95% CI: 0.32 - 0.99) or negative (N=50, HR 0.73, 95% CI: 0.42 - 1.25) and those whose tumors were positive for PD-L1 staining at ≥1% (HR: 055; 95%CI: 0.36-0.83) vs. ≤1% (HR: 0.89 95% CI: 0.54-1.45).[59] Also at ASCO, updated efficacy data for pembrolizumab in recurrent/metastatic SCCHN (KEYNOTE-012) was presented. An overall objective response rate (ORR) of 18% (34/192; 95% CI: 13-24%) was observed, with ORR of 24% (11/45, 95% CI: 13 - 40%) and 16% (23/147, 95% CI: 10 – 23%) in HPV-positive and HPV-negative patients, respectively. However, the limited number of patients evaluated and overlapping 95% CIs preclude definitive conclusions regarding any role HPV or PD-L1 status may play in response to checkpoint inhibitor treatments. Additionally, it should be noted that both HPV groups had the same (n=4) number of patients with CR in the KEYNOTE-012 update. Median time to response was 2 months, but several patients took substantially longer to respond (range: 2 - 17 months). Median OS was 8 months (95% CI: 6 – 10 months) in these heavily pretreated patients with 38% alive at 12 months.[60,61] These trials provide strong early evidence that SCCHN represents a tumor type that is responsive to this class of agents. Collectively, these data, the strong scientific rationale for radiation (which increases PDL-1 expression) and immune checkpoint inhibitor combinations, and the poor patient options if disease control is not obtained in front-line therapy, persuasively argue for progressing an immune checkpoint inhibiting agent into combination therapy with definitive CRT to provide an optimized, multimodality approach to treat this disease and help patients avoid the high morbidity and mortality associated with disease progression. This combination can potentially overcome the treatment resistance that patients experience, in particular for HPV-negative tumors.[43]

1.2.3.2. Rationale for Chemoradiotherapy Dose

Definitive locoregional therapy combined with systemic chemotherapy is the current SOC for locally-advanced SCCHN based upon multiple randomized trials.[10,13,44] Definitive radiation therapy treats the extent of local tumor, including any involved lymph nodes, and is combined with concurrent chemotherapy. Radiation therapy dose for areas of gross tumor is defined by the maximally tolerated dose to the surrounding normal tissue and is commonly noted as 70 Gy/35 fractions/7 weeks; 1 fraction/day, 5 fractions/week.[36] The optimal chemotherapy regimen is not defined, but cisplatin is the most commonly used agent and is known to be a radiosensitizing agent. The delivery of chemotherapy in conjunction with radiation (vs. induction or adjuvant alone) is well supported by the individual patient data meta-analysis, MACH-NC (Meta-analysis of Chemotherapy in Head and Neck cancer), which reviewed almost 16,500 patients' data and demonstrated an HR of 0.81 of CRT vs. definitive radiation alone, producing an absolute survival advantage of 6.5% at 5 years. This was limited to concurrent chemotherapy and not shown for either induction or adjuvant. Thus, definitive radiation therapy with cisplatin administered Q3W at 100 mg/m^2 is considered a SOC and is commonly used in clinical trials as such.

Complete information for cisplatin may be found in the SRSD, which for this study is the cisplatin package insert.[37]

1.2.3.3. Rationale for Avelumab Dose and Schedule in Regards to CRT Regimens to be Evaluated

In this clinical trial, the avelumab dose will be 10 mg/kg administered as 1-hour IV infusions. Avelumab (or placebo) will be administered on Day 1 of the Lead-in Phase; Days 8, 25, and 39 in conjunction with SOC CRT during the CRT Phase; and Q2W for 12 months during the Maintenance Phase.

Avelumab 10 mg/kg Q2W is the recommended dosing regimen and has been administered to a total of 1738 patients in the ongoing dose-expansion phase of Study EMR100070-001 (see Section 1.2.2 for details).

1.2.3.3.1. Rationale for Concurrent Administration of Avelumab with CRT Followed by Maintenance with Avelumab

The combination of avelumab and radiation therapy with concurrent cisplatin has not been evaluated in nonclinical pharmacology, pharmacokinetics and metabolism, or toxicology studies. However, a strong scientific rationale exists for combining avelumab with radiation therapy.[17,18,19] The combination of anti-PD-L1 with commonly used cancer treatments, such as cytotoxic agents and RT, resulted in an improved anti-tumor activity in animal models as noted previously. In particular, radiation therapy in combination with avelumab was found to be highly synergistic, capable of causing complete regression of established tumors with the potential to generate anti-tumor immune memory.[17]

Multiple lines of evidence suggest that following immune checkpoint inhibition therapy (anti-PD-1, PD-L1, CTLA-4, or a combination thereof), T-cell mobilization and proliferation is evident in the periphery by approximately 14 days post-treatment and intratumorally by a median of 39 days post-treatment.[38] Dosing avelumab 7 days prior to initiation of CRT (Day 1 of Lead-in Phase) may effectively activate and initiate expansion of T-cell populations which are receptive/reactive to antigens released by CRT and protect these sensitive T-cell populations from radiation by mobilizing them to the periphery, thereby maximizing the potential antitumoral response upon administration of CRT on Day 8 of the CRT Phase.

There is preclinical evidence of enhanced efficacy of PD-L1 agents with radiation when given concurrently that is greater than the benefit seen in the models when PD-L1 therapy is only initiated at the conclusion of RT; however, there is still benefit when the therapies are given sequentially over tumor control with RT alone.[35,39] Therefore, the maximize potential benefit of the addition of avelumab to CRT, avelumab will be delivered in all 3 treatment settings where benefit may be achieved: the 1) Lead-in Phase, 2) CRT Phase, and 3) Maintenance Phase.

The ideal schedule is neither known, nor are there studies that define the optimal length of maintenance therapy in this front-line treatment setting. Also, in the metastatic setting, treatment duration is not well studied. Most PD-1/PD-L1 regimens have been arbitrarily limited at 2 years of treatment. Anecdotal evidence exists for long duration of response after discontinuation of treatment, as well as responses after re-treatment in patients who have progressed after initial benefit. There are data supporting the concept of immune response

induction with the initial treatments, and then the maintenance phase prolongs and supports the immune memory development.[58] Thus, a schedule was designed to dose avelumab for a sufficient length of time to enrich the likelihood of patient response, without being overly extended in the Maintenance Phase for multiple years as a substantial number of patients might have already achieved maximal response within the year of maintenance.

1.2.3.4. Rationale for Selected Patient Population

This study is designed to determine the effect of avelumab in combination with SOC CRT compared to SOC CRT alone for patients with high-risk disease and a relatively poor prognosis with current SOC. The proposed patient population will include patients with previously untreated locally advanced SCCHN in the following stages: HPV-negative SCCHN patients with Stage III, IVa, or IVb disease, HPV-positive SCCHN patients from non-oropharyngeal sites with stage III, IVa, or IVb disease and high risk HPV-positive SCCHN patients with oropharyngeal SCCHN as evidenced by T4 or N2c or N3 disease. Although patients with an HPV-positive oropharyngeal tumor have an overall better prognosis than patients with an HPV-negative tumor and the same stage, the most advanced stages of HPV-positive locoregional disease, still carry a poor outcome with current SOC. Therefore, HPV-positive SCCHN patients with oropharyngeal T4or N2cor or N3 disease will be included, as SCCHN patients with these stages of disease are still considered high risk and with a poor prognosis based on a systematic review by ICON-S (International Collaboration on Oropharyngeal Cancer Network for Staging).[40,41] HPV-related disease in other primary tumor locations is much less common and there are insufficient data to indicate that prognosis would be altered. These subgroups of patients are at highest risk for recurrence and therefore, represent appropriate populations for a clinical trial investigating additional treatment over SOC.

1.2.3.5. Rationale for Stratification Factors

The selection of randomization stratification factors for this study took into consideration both the size of the study and the prognostic impact of the factors on the primary endpoint. Tumor stage and nodal stage were selected as the randomization stratification factors for this study as each factor confers a different prognostic outcome for patients, which correlates directly with PFS.[42]

HPV status in oropharyngeal cancer is associated with a different prognostic outcome under current treatment SOC.[41] Thus, this trial will only enroll patients with high-risk HPV-positive disease who have poor prognosis with current SOC. There are currently no data as to whether HPV status itself will impact responsiveness to immune checkpoint inhibition in combination with SOC CRT in this indication, although emerging response data from studies of single-agent immune checkpoint blockade in the recurrent/metastatic setting do not suggests such a difference. As described previously, pembrolizumab was reported to have approximately a 25% ORR in the recurrent/metastatic setting, with ORRs of approximately 21% and 27% in patients with HPV-positive and HPV-negative disease, respectively. No difference in response between patients with HPV-positive vs HPV-negative tumors were observed, although the overall number of patients evaluated in this study was small. These data from the recurrent/metastatic treatment setting have limited applicability, as they do not account for the radiation impact, and are limited overall.

Preclinical data are equally uninformative. Thus, stratifying on the basis of HPV status will ensure equal distribution of HPV-positive SCCHN patients in each treatment arm should any differential impact of immune checkpoint inhibition with SOC CRT exist.

1.2.3.6. Rationale for Endpoints

Cancers of the head and neck region are somewhat unusual in their relative accessibility for direct observation of response or recurrence that may not be as clear on radiologic imaging. Disease recurrence may be visible on inspection of the head and neck mucosal surfaces that does not cause any radiologically visible changes. Conversely, radiologic changes may occur that arise as a consequence of acute tissue response to local therapy (ie, CRT) that are radiographically indistinguishable from tumor progression changes. This patient population is also at higher risk at developing second primary malignancies due to the common etiologic risks of tobacco and excessive alcohol intake. Therefore, tumor-related endpoints in this study will be based on Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 modified with respect to the definition of what constitutes progressive disease (PD) as detailed in Section 3.2, Section 9 and Appendix 3. Broadly, locoregional disease progression requires biopsy confirmation and biopsies are strongly recommended to confirm a diagnosis of distant metastatic progression. Per current standard patterns of care, neck dissection completed with 140 days following completion of CRT is considered part of the definitive management of the tumor and not as a disease progression event.

1.3. Summary of Benefit/Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

The benefit-risk relationship has been carefully considered in the planning of the trial. Avelumab has demonstrated clinical activity in patients with advanced solid tumors in an expansion cohort of an ongoing Phase 1 Trial EMR 100070-001. The clinical safety data with single-agent avelumab in patients with advanced solid tumors available to date suggest an acceptable safety profile of the compound and no differences in the overall safety profile for patients with SCCHN relative to all patients. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with those observed with other antibodies blocking the PD-1/PD-L1 axis (see Section 1.2.2.1). Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a histamine H1 receptor (H1) blocker and acetaminophen. Risk mitigation measures for AEs associated with CRT are discussed in their respective sections.

As reported by Ang et al. from Study RTOG0522, among patients with previously untreated Stage III to IV squamous cell carcinoma of the oropharynx, hypopharynx, or larynx treated with combination of radiotherapy over 6 weeks, and cisplatin (100 mg/m^2 on Days 1 and 22 of radiotherapy) (N=447), Grade 3-4 treatment-related toxicities were reported in 87% of

patients.[44] The most commonly reported Grade 3-4 non-hematological toxicities involved the gastrointestinal tract and included adverse events of dysphagia (57%), radiation mucositis (33%), mucositis/stomatitis of pharynx (24%), dehydration (15%), nausea (14%), and vomiting (9%). Skin reactions inside the portal were reported in 79% of patients (all severity grades) with 15% of patients experiencing Grade 3/4 events. The most frequently reported hematological toxicities included leukopenia (19%), neutrophil count decreased (16%), and lymphopenia (13%).[43,44]

The safety profile, consistent with Study RTOG0522, was reported among 361 patients treated on Study RTOG0129 with newly diagnosed stage III to IV carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx treated with a combination of radiotherapy (standard fractionation [70 Gy in 35 fractions over 7 weeks]) in combination with cisplatin 100 mg/m^2 once every 3 weeks for 3 cycles. Grade 3 to 5 toxicities were reported in approximately 80% of patients. The most common Grade 3 to 5 toxicities reported were gastrointestinal (approximately 60%), including radiation mucositis, dysphagia, nausea, vomiting, and dehydration. Blood/bone marrow toxicities were reported in approximately 40% of patients most notably leukopenia/neutropenia. Overall radiation dermatitis (all severity grades) was reported in approximately 70% of patients with severe radiation dermatitis (all Grade 3) was reported in 8% of patients.[45]

The safety profile of avelumab is described in Section 1.2.2.1 of this document and the Avelumab Investigator's Brochure, version 7.0.[17] Identified risks include immune-mediated reactions and infusion-related reactions. No events of mucositis have been reported among 1738 patients from the Pooled Safety Dataset. Grade 3 to 4 neutropenia and leukopenia were reported in ≤1% of patients. Severe immune-related rash was uncommon with avelumab treatment (0.1%).

Additional safety concerns are not expected from combining avelumab with radiotherapy, given their distinct mechanisms of action and toxicity profiles, consistent with the existing literature on concurrent immunotherapy with radiation therapy. A retrospective analysis by Barker et al described findings among 29 patients treated with ipilimumab (median dose 10 mg/kg) for melanoma who underwent non-brain radiotherapy (median dose 30 Gy) between the first and last doses of ipilimumab. In this study, the rates of local adverse events (AEs) or systemic immune-related irAEs were not increased with the concurrent treatment of ipilimumab and radiotherapy.[46]

In a Phase 1/2 study in metastatic castration-resistant prostate cancer, patients received ipilimumab 10 mg/kg, with (n=34) or without (n=16) radiotherapy. Grade 3/4 treatment-related AEs were reported in 38% and 63% of patients treated with and without concurrent radiotherapy respectively. Similarly, Grade 3/4 irAEs were reported in 18% and 63% of patients, respectively. No increased toxicity was noted among patients treated with ipilimumab and concurrent radiotherapy.[47]

Given the distinct safety profile and mostly non-overlapping toxicities, no significant increased risk is anticipated from the combination of avelumab with CRT including cisplatin for the treatment of locally-advanced SCCHN. The potential for benefit is significant given

the strong preclinical interaction between radiation and immune checkpoint inhibitors as well as the data showing activity as single agents, which in the frontline setting could result in enhanced localregional tumor control and improved PFS and OS. As described previously, treatment options for patients with recurrent SCCHN are limited and associated with severe toxicities; response rates are low, ranging between 15% and 36% with a median OS of 6 to 10.1 months. Improved treatment for locally-advanced, high-risk SCCHN to prevent locoregional relapse and distant metastases is critical for successful management of this multidimensional disease and therefore testing of multimodality therapy is appropriate with an acceptable risk-benefit profile for patients.

The Sponsor plans to closely monitor the safety profile for new emerging safety risks or increased frequency or severity of anticipated risks based on a review of aggregate data.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

To demonstrate that treatment with avelumab in combination with SOC CRT is superior to SOC CRT alone in prolonging PFS in front-line patients with high risk (as defined in Inclusion Criterion 2 [Section 4.1]), locally advanced SCCHN who are candidates for definitive CRT with cisplatin.

Secondary Objectives

- To compare the OS of avelumab in combination with SOC CRT vs SOC CRT alone.
- To evaluate the anti-tumor activity of avelumab in combination with SOC CRT and SOC CRT alone.
- To evaluate the overall safety and tolerability profile of avelumab in combination with SOC CRT and SOC CRT alone.
- To evaluate the PK of avelumab.
- To evaluate the PK of cisplatin (total and free).
- To assess avelumab ADAs.
- To evaluate the effect of avelumab in combination with SOC CRT and SOC CRT alone on patient-reported outcomes (PROs) of disease-related symptoms and health-related quality of life.
- To evaluate candidate immune-related predictive biomarkers of sensitivity or insensitivity to treatment with avelumab in combination with SOC CRT in pre-treatment tumor samples (eg, PD-L1 expression).

- To evaluate candidate immune-related predictive biomarkers of sensitivity or insensitivity to treatment with avelumab in combination with SOC CRT in tumor samples (eg, PD-L1 expression) after one dose of avelumab in patients who provide this optional biopsy.

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[redacted]

2.2. Endpoints

Primary Endpoint

- PFS per modified RECIST v1.1 (see Appendix 3 for specific modifications, including pathologic confirmation) by investigator assessment.

Secondary Endpoints

- OS.
- *Antitumor activity:* Pathologic complete response in any resected specimens, neck dissection.
- *Antitumor activity:* Locoregional failure, objective response, distant metastatic failure, and duration of response, per modified RECIST v1.1 by investigator assessment.
- *Safety:* Adverse events and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; vital signs (blood pressure, pulse rate).
- *Pharmacokinetics:*
  - C_{max} and C_{trough} for avelumab;
  - Area under the concentration-time curve extrapolated to infinity (AUC_{inf}), C_{max}, clearance (CL), time to maximum plasma concentration (T_{max}), elimination

half-life ($t_{1/2}$), and volume of distribution (V_z) for cisplatin (total and free), as data permit.

- *Immunogenicity:* ADA (neutralizing antibody) against avelumab.
- *Patient-Reported Outcomes:* Disease-related symptoms and Health-Related Quality of Life as measured by the National Cancer Comprehensive Network (NCCN) Head and Neck Symptom Index-22 items (FHNSI-22), and the EuroQoL Group 5-Dimension 5- Level Self-Report Questionnaire (EQ-5D-5L).
- *Biomarkers:* Tumor tissue biomarkers including but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T-lymphocytes.

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[redacted]

3. STUDY DESIGN

3.1. Overall Study Design

This is a Phase 3, international, multicenter, randomized, double-blind, parallel, 2-arm study in patients with previously untreated, histologically confirmed locally advanced SCCHN (oral cavity, oropharynx, larynx, or hypopharynx) who are candidates for definitive CRT with cisplatin.

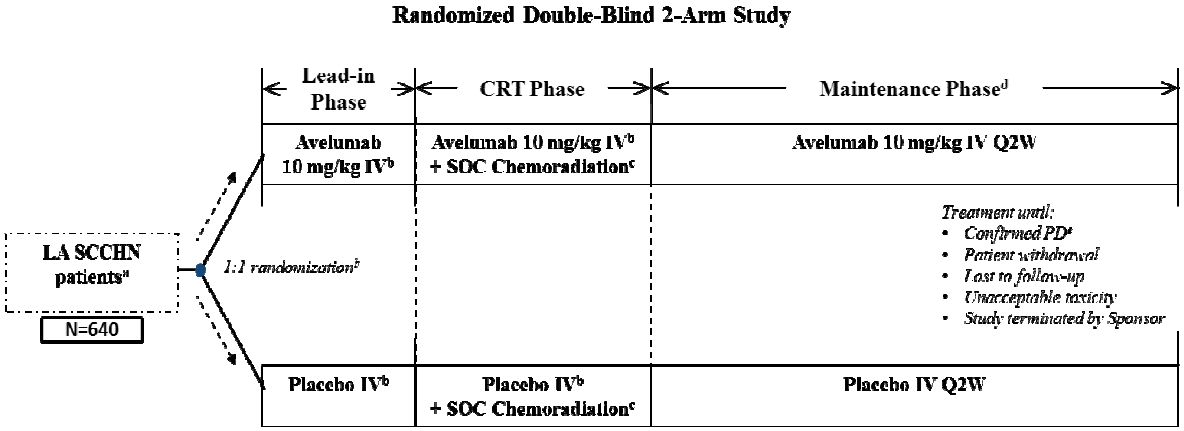
The study is designed with the primary objective of demonstrating that treatment with avelumab in combination with SOC CRT is superior to SOC CRT alone in prolonging PFS.

One interim analysis for the assessment of PFS will be conducted to allow early stopping of the study for futility or to demonstrate early superiority of avelumab in combination with SOC CRT compared to SOC CRT alone, and to assess the safety of avelumab in combination with SOC CRT.

A total of approximately 640 patients will be randomized in a 1:1 ratio to either Arm A (avelumab + SOC CRT) or Arm B (placebo + SOC CRT). Randomization will be stratified by tumor (T) stage (<T4 vs T4), nodal (N) stage (N0/N1/N2a/N2b vs N2c/N3), and HPV status (positive vs negative) as measured by p16 expression by IHC.

The study schematic is provided in Figure 3.

Figure 3 Study Design



a. Patients with LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx) eligible for front-line treatment: HPV negative disease stage III, IVa, IVb; non-oropharyngeal HPV positive disease stage III, IVa, IVb; HPV positive oropharyngeal disease T4 OR N2cOR N3 (staging per TNM [tumor, node, metastases] guidelines for head and neck sites AJCC 7th Edition). (Note: entry criteria for patients with HPV-positive tumors are different than for HPV-negative tumors).

b. Avelumab or placebo IV to be administered on Day 1 of the Lead-in Phase (1 week prior to the start of the CRT Phase), and on Days 8, 25, and 39 during the CRT Phase.

c. SOC CRT = IMRT (70 Gy/35 fractions/7weeks; 1 fraction/day, 5 fractions/week) for 7 weeks + cisplatin (100 mg/m^2 Days 1, 22, 43) during the CRT Phase.

d. Maintenance Phase to start after completion of the CRT Phase and continue for 12 months.

e. Patients will continue treatment until confirmed disease progression as assessed by Investigator per modified RECIST v1.1.

AJCC = American Joint Committee on Cancer; CRT = chemoradiotherapy; HPV = human papillomavirus; IMRT = intensity-modulated radiation therapy; LA = locally advanced; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SCCHN = squamous cell carcinoma of the head and neck; SOC = standard of care.

There will be 3 treatment phases in this study.

- Lead-in Phase: On Day 1 of the Lead-in Phase of the study, patients will receive a single dose of avelumab or matching placebo, administered 7 days prior to initiation of the CRT Phase;

- CRT Phase: Avelumab or matching placebo will be administered on Days 8, 25, and 39 in conjunction with SOC CRT starting on Day 1 of the CRT Phase;

- Maintenance Phase: Following completion of the CRT Phase, avelumab or matching placebo will be administered Q2W for 12 months during the Maintenance Phase.

The treatment schedule is described in the following table.

Table 4. Chemoradiation and Avelumab/Placebo Treatment Schedule

	Lead-in Phase (7 days)[a]	CRT Phase (63 days)									Maintenance Phase[b]
	-- Day --	---------- Day ----------									
	1	1	8	15	22	25	29	36	39	43	
IMRT (70 Gy/35 fractions/7 weeks; 1 fraction per day, 5 fractions/week [Monday – Friday])		X→	X→	X→	X	→	X→	X→	→	X→	
Cisplatin (100 mg/m^2 Q3W)		X			X					X	
Avelumab (10 mg/kg) or placebo	X		X			X[c]			X		Q2W

a. Lead-in Phase to start 7 days prior to initiation of CRT Phase.
b. Maintenance Phase to start after completion of the CRT Phase (ie, 2 weeks following completion of CRT) and be 12 months in duration. CRT phase may be extended as required for patient recovery from CRT; however, it is hypothesized that patients will receive maximal benefit from beginning maintenance as close to the scheduled time as possible.
c. Day 25 dose of avelumab/placebo during the CRT Phase may be administered between Day 24 and Day 29.

Cisplatin should be administered on a Monday or Tuesday if feasible to maximize overlap with IMRT.

CRT = Chemoradiotherapy; IMRT = intensity-modulated radiation therapy; Q2W = every 2 weeks; Q3W = every 3 weeks.

NOTE: The study consists of 3 study treatments: avelumab/placebo as study treatment 1; cisplatin as study treatment 2; IMRT as study treatment 3. Cisplatin is not to be considered concomitant medication.

Patients who meet all study entry criteria will be randomized 1:1 to study treatment (Arm A or Arm B). Patients will receive study treatment until completion of the protocol-defined treatment period (ie, 12 months following completion of CRT Phase), PD per modified RECIST v1.1, patient withdrawal of consent, patient lost to follow-up, or until unacceptable toxicity occurs, or until the study is terminated by the Sponsor, whichever occurs first.

If a patient starts a new anti-cancer therapy prior to disease progression per modified RECIST v1.1, tumor assessments should be continued per Schedule of Activities (unless not feasible) until PD per modified RECIST v1.1 or death.

All patients will be followed for survival until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new cancer therapy. All patients will be followed for safety with evaluations through 90 days after the last study treatment administration or until the time of initiation of new systemic anticancer treatment. The Day 90 Short-Term Follow-up Visit will be conducted as a phone call. If any concern arises, the patient will be called in for a follow-up visit within 5 calendar days of the initial phone call for appropriate assessment (as per the investigator's medical judgement). Beyond the Day 90 Short-Term Follow-up Visit, all patients will be followed every 16 weeks (Q16W) for survival and new systemic anticancer treatment within the long-term follow-up period.

Patients who refuse to return to the site for evaluations should be contacted by telephone as an alternative.

3.2. Tumor Assessments

- Tumor assessments will be completed on the schedule detailed below using a modification of RECIST v1.1. The modification is required in head and neck cancer assessment as these tumors are fairly unique in their accessibility for thorough clinical evaluation and biopsy. Furthermore, the extensive mucosal surface which is available for clinical evaluation of tumor response or recurrence may indicate tumor status changes that may not be present or as clear on radiographic imaging alone. Conversely, radiographic changes that could be suggestive of tumor progression or recurrence can reflect radiation therapy changes. Taken collectively, this has given rise to the clinical practice of using biopsies to directly assess tumor recurrence in this patient population. Therefore, RECIST was modified for this protocol to recognize this practice and better confirm (through direct pathologic ascertainment) when tumor recurrence has occurred.

- Radiographic and clinical evaluations will be conducted with the same schedule in both treatment arms of the study. The investigator will assess antitumor activity based on radiological assessments and clinical evaluation of patients using modified RECIST v1.1 (see Appendix 3) at baseline, 12 weeks after the completion of CRT, every 16 weeks (Q16W) thereafter for 48 months (208 weeks), and every 24 weeks (Q24W) thereafter until confirmed disease progression per modified RECIST v1.1 and regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy.

- Radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or physical exam findings suggestive of mucosal recurrence).

- Locoregional disease progression per modified RECIST v1.1 requires that radiographic changes suggestive of disease progression are confirmed by biopsy. Pathologic confirmation of progression will verify that radiographic changes represent true tumor progression and not radiation effects or non-malignant contrast enhancement.

- When disease progression occurs for distant metastases per RECIST v1.1, confirmation of pathology is recommended unless medically contraindicated or if the lesion location is too high risk for biopsy.

- If a patient withdraws from study treatment for a reason other than disease progression per modified RECIST v1.1, radiological tumor assessments are to continue until disease progression per modified RECIST v1.1 even if a new anti-cancer therapy is initiated.

- A head and neck CT or MRI, chest CT, and PET scan are required at baseline and at 12 weeks after completion of CRT. High resolution PET/CT does not require additional CT thorax/neck/brain. MRI brain may be performed if clinically indicated. Subsequent PET scans may be performed during the Maintenance Phase in the absence of clinical or CT complete resolution of nodal disease (described in Section 3.3) or at the investigator's discretion. Baseline tumor assessments should be done within 28 days prior to randomization.

3.3. Tumor Related Endpoints and Definitions

Tumor related endpoints in this study will be based on RECIST v1.1 modified with respect to the definition of what constitutes **progressive disease** (PD) as follows. Any of the following will constitute PD per modified RECIST v1.1:

- Locoregional disease progression per RECIST v1.1 which is subsequently confirmed by pathology. Pathologic confirmation of progression will verify that radiographic changes represent true tumor progression and not radiation effects or non-malignant contrast enhancement.

- Locoregional clinically detectable progression that is confirmed by pathology.

- Surgical removal (salvage) of primary tumor with tumor present on final pathology.

- Salvage neck dissection >20 weeks (140 days) after completion of CRT with tumor present on final pathology.

- Metastatic (distant metastases) disease progression per RECIST v1.1. Confirmation of pathology is recommended unless medically contraindicated or lesion location too high risk for biopsy.

Pathologic evaluation of resected or biopsied specimens must be completed by a trained and medically qualified expert (eg, specialty board certified pathologist).

Pathologic complete response is defined as the absence of histologically identifiable residual cancer in any resected specimen.

Local failure is defined as residual or recurrent viable tumor on pathologic evaluation from the site of original tumor location. Presence of tumor is required for declaration of a progression event which requires identification of viable tumor cells on final pathology. Tumor reappearing within the initial and immediately adjoining anatomical region of the primary will be considered local recurrence.

Regional failure is defined as residual or recurrent viable tumor on pathologic evaluation from the regional lymph node basins (eg, neck nodes). Presence of tumor is required for declaration of a progression event which requires identification of viable tumor cells on final pathology.

Distant metastatic disease is defined as new tumor identified at a site distant from the head and neck anatomic region or draining lymph nodes. Biopsy of any presumed distant metastatic disease is strongly recommended. A solitary, speculated lung mass/nodule is a second primary neoplasm and is not a disease progression event unless proven otherwise by biopsy in a patient with a smoking history. Multiple lung nodules/masses are considered distant metastases from the index cancer and constitute a disease progression event unless proven otherwise by biopsy.

Irradiation of the primary tumor and radiographically enlarged lymph nodes is considered part of the treatment under investigation in this clinical trial and therefore these target lesions remain evaluable lesions for response assessment.

It is expected that the status of the primary tumor is assessed thoroughly at the beginning of the surgical procedure before undertaking nodal dissection. Presence of persistent disease at the primary site, confirmed by frozen section will be considered disease progression.

Neck dissection parameters are described in Section 3.4 and will consist of a selective neck dissection unless a cytologic sampling of the nodes that appear enlarged is negative.

Positive neck specimens removed within 140 days after completion of CRT will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures.

3.4. Surgical Salvage of Residual Disease after Completion of the CRT Phase

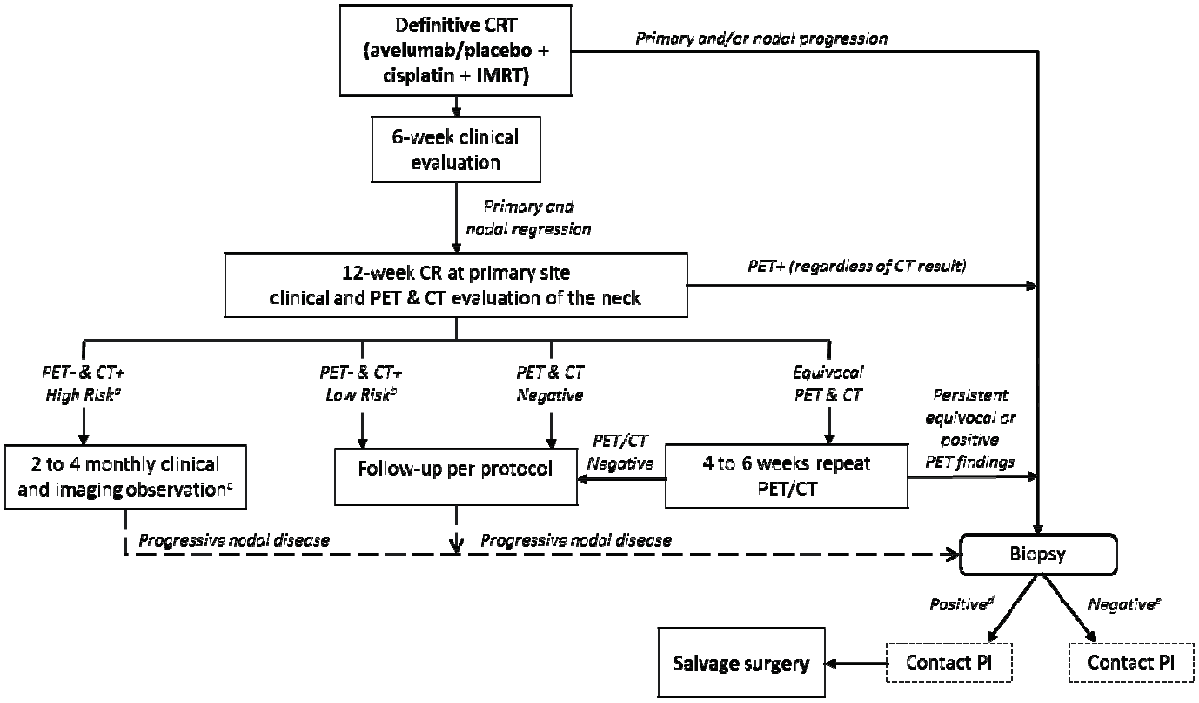
Treatment of residual disease at the primary site will be determined by the investigator and the clinical situation (see Figure 4). If treatment at the primary site is necessary after completion of CRT, study treatment has failed and the patient will discontinue the study treatment. Surgical resection, re-irradiation, chemotherapy, or palliative care may be performed per institutional policy. If the primary site is cleared of residual disease yet residual disease at the cervical nodal basin is suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling of the node is negative. Residual disease in the neck is not considered a treatment failure if surgical salvage is completed within 140 days of completion of CRT. A primary treatment neck dissection after completion of the CRT Phase will be defined as a neck dissection performed for residual disease and within 20 weeks (140 days) of completion of CRT. Patients who undergo such a primary treatment neck dissection will not be considered experiencing a disease progression event and remain on study treatment, regardless whether neck specimens are positive or negative.

Positive specimens removed within 140 days of completion of CRT will be considered part of the initial treatment plan and not considered failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures. Such consolidation neck dissections after completion of the CRT Phase will encompass only the areas (typically only levels 2 and 3) initially involved in the side of the neck in question. The extent of neck dissections performed for nodal recurrence or nodal progression, and/or salvage of disease at the primary will be determined by the treating surgeon.

If a neck dissection is required, then the treating surgeon is required to contact the surgical Principal Investigator (PI) of this study, Dr. PPD) prior to the surgery to discuss the clinical and radiologic findings as well as the planned surgery itself. Notes from the surgery, as well as the pathology report from the neck dissection, must also be submitted to Dr. PPD for review when they become available, but no later than 6 weeks following the procedure.

In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal CR at the tumor assessment performed 12 weeks following completion of CRT, follow-up PET scans are recommended every 4 months (Q16W) with the CT imaging for 24 months, then every 6 months (Q24W) in Years 3-5, as well as careful recording of the clinical dimensions of the residual abnormality. CT imaging should be obtained as described in the Schedule of Activities beyond Year 5.

Figure 4 Algorithm for Evaluation of Regional Lymph Nodes Following Definitive CRT



a. High risk = perceived risk of residual disease is high, such as sub-optimally treated patients due to premature cessation of treatment, unplanned treatment interruptions.
b. Low risk = perceived risk of residual nodal disease is low, such as low burden disease without treatment interruption.
c. Ongoing clinical and imaging observation until residuum is <1 to 1.5 cm or stable for >6 months.
d. In the case of positive biopsy, the surgical PI (Dr. PPD]) must be contacted prior to performing the surgery to discuss the clinical and radiological findings as well as the planned surgery itself.
e. If biopsy is negative but there is high clinical/radiologic suspicion of disease, consider re-biopsy and contact the surgical PI (Dr. PPD]) for discussion.

CRT = chemoradiotherapy; CT = computed tomography; IMRT = intensity-modulated radiation therapy; PET = positron emission tomography; PI = (surgical) principal investigator.

3.5. Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as described in the Schedule of Activities table.

3.6. Pharmacokinetic/Immunogenicity Assessments

Samples for PK and immunogenicity analyses will be collected as described in the Schedule of Activities table.

3.7. Biomarker Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and SOC CRT. In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action, as well as potential mechanisms of resistance, to the combination of avelumab with SOC CRT. Tumor and blood biospecimens as required for the various analyses will be collected as described in the Schedule of Activities table.

3.8. Patient-Reported Outcomes

Patient-Reported Outcomes (PRO) will be assessed using the NCCN FHNSI-22[48] and the EQ-5D-5L[49] CCI [redacted] The maximum number of questions to be answered at any assessment is 30, so PRO collection is not expected to be burdensome to patients. The EQ-5D-5L will be administered to assess overall quality of life and to produce the utility values used for the economic model. The NCCN FHNSI-22 will be administered specifically to capture head and neck related (disease-related [DRS]) physical (DRS-P) and emotional symptoms (DRS-E), treatment side effects (TSE), and functional well-being (FWB), with a focus on the item "I can swallow naturally and easily." CCI [redacted]

The EQ-5D-5L, FHNSI-22, CCI [redacted] will be administered on Day 1 of the Lead-in Phase (baseline); Days 1 and 29 of the CRT Phase; on Day 1 Cycle 1 and Day 1 Cycle 3 during the Maintenance Phase; then Q16W for 48 months, then Q24W until PD per modified RECIST v1.1. CCI [redacted]

CCI [redacted]

3.8.1. NCCN-FHNSI-22

The NCCN FHNSI-22 was developed using methods consistent with the Food and Drug Administration (FDA) PRO guidance[50] and surveyed input from patients with advanced cancers and physician experts.[48] The FHNSI-22 questionnaire is specifically designed to be a stand-alone instrument to measure disease symptoms, treatment side effects and overall quality of life in patients with head and neck cancer.

Responses on the FHNSI-22 questionnaire are used to calculate a total score and scores for four subscales: TSE, DRS-P, DRS-E, and FWB. The questionnaire contains 22 items with 5-point Likert scales ranging from 'not at all' to 'very much'. Higher scores mean better symptomatology, quality of life or functioning. The expected questionnaire completion time is about 5 minutes.

3.8.2. EQ-5D-5L

The EuroQol EQ-5D-5L is a patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[49] There are 2 components to the EuroQol EQ-5D-5L: a descriptive system in which individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self- care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score for the 5 Likert scale items. The expected questionnaire completion time is about 3 minutes or less.

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4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

4. Histological diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx with tissue available.

5. High-risk disease as defined by American Joint Committee on Cancer [AJCC] Guidelines 7th Edition:[42]

   - HPV-negative disease, Stage III, IVa, IVb per tumor/nodes/metastasis (TNM) guidelines for head and neck sites; or
   - Non-oropharyngeal HPV-positive disease, Stage III, IVa, IVb per TNM guidelines for head and neck sites; or
   - HPV-positive oropharyngeal disease T4 OR N2c OR N3 per TNM guidelines for head and neck sites.

   where HPV status will be determined per institutional standard using p16 immunohistochemistry (IHC).

6. No prior therapy for advanced stage SCCHN; eligible for definitive CRT with curative intent.

7. Available tumor samples for submission or willing to undergo further tumor biopsies:

   - Availability of a formalin-fixed paraffin-embedded (FFPE) tumor tissue block from primary tumor or nodal biopsy. If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable.

8. Age ≥18 years (≥20 years in Japan and Taiwan, and ≥19 years in Korea).

9. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1 (Appendix 2).

10. Adequate bone marrow function, including:

    - Absolute Neutrophil Count (ANC) ≥1,800/μL or ≥1.8 x 10^9/L.
    - Platelets ≥100,000/μL or ≥100 x 10^9/L.
    - Hemoglobin ≥9 g/dL (may have been transfused).

11. Adequate renal function, including:

    - Estimated creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault (CG) equation OR;
    - A creatinine clearance of at least 60 ml/min if this value is described in the contra-indications for cisplatin as per country's local labeling.

12. Adequate liver function, including:

    - Total serum bilirubin ≤1.5 x upper limit of normal (ULN).
    - Aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x ULN.

13. Pregnancy test (for patients of childbearing potential) negative at screening.

14. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two methods of contraception (at least one of which is considered to be highly effective as defined in Section 4.3) throughout the study and for at least 6 months after the last dose of cisplatin and 30 days after the last dose of avelumab/placebo (whichever is later).

    Female patients who are not of childbearing potential (ie, meeting at least one of the following criteria):

    - have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - have medically confirmed ovarian failure;
    - have achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause. Status may be confirmed by a serum follicle-stimulating hormone (FSH) level consistent with the post-menopausal state.

15. Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative, as allowed by local guideline/practice) has been informed of all pertinent aspects of the study.

16. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Prior immunotherapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways.

2. Major surgery ≤4 weeks prior to randomization.

3. Prior malignancy (other than the current Head and Neck cancer or in situ disease) requiring tumor-directed therapy within the last 2 years prior to enrollment, or concurrent malignancy associated with clinical instability. Exceptions for disease within the 2 years are superficial esophageal cancer (TIS or T1a) fully resected by endoscopy, prostate cancer (Gleason score ≤6) either curatively treated or deemed to not require treatment, ductal in situ carcinoma of the breast that has completed curative treatment, adequately treated basal cell or squamous cell skin cancer.

4. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

5. Any of the following in the 6 months prior to randomization: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism.

6. Active infection requiring systemic therapy.

7. Known prior severe hypersensitivity to investigational products or any component in the formulations, including known severe hypersensitivity reactions to mAbs, cisplatin, or platinum-related compounds (NCI CTCAE v4.03 Grade ≥3).

8. Use of immunosuppressive medication at time of randomization, except the following:

    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);

    b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;

    c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

9. Prior organ transplantation including allogenic stem-cell transplantation.

10. Diagnosis of prior immunodeficiency or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.

11. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA [ribonucleic acid] if anti-HCV antibody screening test positive).

12. Vaccination within 4 weeks prior to randomization except for administration of inactivated vaccines.

13. Current use of or anticipated need for treatment with other anti-cancer drugs.

14. Pregnant female patients, breastfeeding female patients, and male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 methods of contraception (at least one of which is considered to be highly effective) as outlined in the protocol for the duration of the study and for at least 6 months after the last dose of cisplatin and 30 days after the last dose of avelumab/placebo (whichever is later).

15. Other severe acute or chronic medical conditions including: immune colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis, or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

16. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

17. Participation in other interventional studies involving investigational drug(s) within 4 weeks prior to randomization.

4.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive radiation and cisplatin and half of these patients will also receive avelumab. The effect of avelumab on reproduction is unknown. Cisplatin can cause fetal harm when administered to pregnant women.

Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined below) throughout the study and continue to do so for at least 6 months after the last dose of cisplatin and 30 days after the last dose of avelumab/placebo (whichever is later). The investigator or his or her designee, in

consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 contraception methods consistently and correctly according to the Schedule of Activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Highly effective contraception methods with low user dependency include (applies to female subjects at risk for pregnancy with their male partners):

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, inserted, injected, implanted).

2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).

3. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

4. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Female patients of non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;

- Have medically confirmed ovarian failure; or

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum FSH level consistent with the post-menopausal state.

All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of study treatment and continuing for at least 6 months after the last dose of cisplatin and 30 days after the last dose of avelumab/placebo (whichever is later).

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

In this study, the investigational products are all study treatments to be administered, namely, avelumab (MSB0010718C)/placebo and SOC CRT. The study treatments include the following:

- Arm A: Avelumab + SOC CRT:
    - Avelumab 10 mg/kg IV: Day 1 of the Lead-in phase; Days 8, 25, and 39 of the CRT Phase; Q2W for 12 months during the Maintenance Phase.
    - Cisplatin 100 mg/m^2 IV: Days 1, 22, and 43 of the CRT Phase.
    - IMRT 70 Gy/35 fractions/7 weeks; 1 fraction/day, 5 fractions/week for 7 weeks during the CRT Phase.
- Arm B: Placebo + SOC CRT:
    - Placebo IV matching avelumab: Days 1 of the Lead-in phase; Days 8, 25, and 39 of the CRT Phase; Q2W for 12 months during the Maintenance Phase.
    - Cisplatin 100 mg/m^2 IV: Days 1, 22, and 43 of the CRT Phase.
    - IMRT 70 Gy/35 fractions/7 weeks; 1 fraction/day, 5 fractions/week for 7 weeks during the CRT Phase.

Note: The Day 25 dose of avelumab/placebo during the CRT Phase may be administered between Day 24 and Day 29.

5.1. Allocation to Treatment

Patients will be randomized in a 1:1 ratio to either Arm A (avelumab + SOC CRT) or Arm B (placebo + SOC CRT). Randomization will be stratified by tumor stage (<T4 vs T4), nodal stage (N0/N1/N2a/N2b vs N2c/N3), and HPV status (positive vs negative) measured by p16 expression by IHC.

Assignment of patient number, patient enrollment, and allocation of study drug will be managed by the Interactive Response Technology (IRT) system (interactive web-based response [IWR]). At the time that a patient has signed informed consent and entered screening, the site should contact the IRT system to obtain the patient identification number. Once a patient has met all eligibility criteria, the site then contacts the IRT system to enroll the patient and to obtain the study drug allocation information. Study treatment must be initiated preferably on the day of randomization, but no later than 3 days after randomization.

At the time of enrollment, site personnel (study coordinator or specified designee) will be required to enter into or select information from the IRT system including but not limited to the user's identification (ID) and password, the protocol number, the patient number, and the date of birth of the patient. The IRT system will then provide a treatment assignment (Arm A or Arm B) and dispensable unit (DU) or vial number. The IRT system will also provide a confirmation report containing the patient number and DU or vial number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Breaking the Blind

At all times, treatment and randomization information will be kept confidential and will not be released to the patient, investigator, the study staff, or the sponsor's study team until following the conclusion of the study, with the exception described in this section.

At the initiation of the study, the study site will be instructed on procedures for breaking the blind. Blinding codes should be broken only in emergency situations for reasons of patient safety. If a patient has an adverse event (AE) that may be considered immune mediated, treatment for the AE should be administered as if the patient is receiving avelumab. Whenever possible, the investigator should contact Pfizer before breaking the blind. The method will be either a manual or electronic process. When the blind for a patient has been broken, the reason must be fully documented. If the blind is broken, the investigator should promptly inform the Pfizer Clinician or Medical Monitor. The patient for whom the blind has been broken will be discontinued from the study treatment and undergo the post-treatment (End-of-Treatment [EOT]/Follow-up) procedures.

5.3. Patient Compliance

All doses of study treatments (avelumab or placebo and SOC CRT) will be administered at the investigational site by well-trained medical staff.

The information related to each trial drug administration, including the date, time, and dose of study drug, will be recorded on the electronic case report form (eCRF). The Investigator will make sure that the information entered into the eCRF regarding drug administration is accurate for each patient. Any reason for noncompliance should be documented.

Noncompliance is defined as a patient missing >1 infusion of any study treatment (avelumab/placebo or cisplatin) for non-medical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance will have been met as well. Non-compliance with radiation is defined in the Radiation Delivery Guidelines Document.

5.4. Investigational Product/Study Treatments Supplies

5.4.1. Radiation Therapy to the Primary Lesion and Neck (IMRT)

5.4.1.1. Dose Specificiations

Radiation therapy (RT) will be delivered using IMRT technique and will be delivered in 35 fractions over 7 weeks, 5 fractions weekly either in one plan (simultaneous integrated boost [SIB]) or through separate plans, of cone-down boosts. Detailed definitions of clinical target volumes to encompass gross disease with appropriate margin (clinical target volume [CTV]1), high risk sub-clinical disease sites (CTV2) and lower risk areas, as well as normal tissue maximal doses are detailed separately in the Radiation Delivery Guidelines Document.

For questions regarding IMRT, please contact Dr. PPD or call PPD.

5.4.1.2. Technical Factors

5.4.1.2.1. Treatment Planning/Delivery

Megavoltage energy photon beam irradiation is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT for cooperative group radiation studies (eg, NRG Oncology, Radiation Therapy Oncology Group [RTOG], or EORT) is acceptable. See Radiation Delivery Guidelines Document for additional details.

5.4.1.2.2. Localization, Simulation, and Immobilization

Patients must have an immobilization device (eg, Aquaplast mask) made prior to treatment planning CT scan.

Although not mandatory, the treatment planning CT scan should be performed with IV contrast so that the major vessels of the neck are easily visualized. However, when possible, fusion of respective diagnostic imaging such as PET/CT and/or MRI should be done to carefully delineate the gross tumor volume. The treatment planning CT scan must be

performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm or less.

5.4.1.3. Documentation Requirements for IMRT

Documentation requirements for IMRT are described in the Radiation Delivery Guidelines Document and include the following:

- Pre-treatment radiation therapy planning CT scan;
- All radiation treatment plans will undergo full, centralized, real-time quality assurance (QA), consisting of a rapid review prior to IMRT initiation and a full review of the delivered plan at the completion of therapy. Details of the IMRT review and treatment plan submission process will be provided in the Radiation Delivery Guidelines Document;
- All treatment plans are to be normalized to provide exactly 95% volume coverage of the PTV1 with 70 Gy.

5.4.1.4. Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks are highly discouraged; however, if necessary for severe acute toxicity, ideally should not exceed 5 treatment days at a time and 10 treatment days in total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness.

Days that the RT department is closed, RT is not expected to be administered and this is not a treatment break. This includes all statutory holidays in that locale. Over times of multiple, consecutive days of holidays, the site is encouraged but not required to "make up" the RT fractions through BID treatments, at least 6 hours apart, during the shortened treatment week.

It is recognized that over the course of 35 treatment fractions in RT various factors aside from statutory holidays may result in RT not being delivered on a day that otherwise could be a potential RT treatment day. It is expected that sites will attempt to keep the overall RT treatment duration as close to 7 weeks as possible, but inability to deliver the RT fraction to a patient on a given day is not a PD unless >2 consecutive regular treatment days (Mon-Fri) are missed. Sites are encouraged to consider BID treatments, at least 6 hours apart, for making up missed RT fractions to maintain the overall treatment time.

RT delivered to the total dose of 70 Gy is a completed dose, regardless of delays in RT delivery.

5.4.2. Cisplatin

All patients will receive cisplatin (100 mg/m^2) administered IV on Days 1, 22, and 43 of the CRT Phase (note: cisplatin given within 48 hours of the scheduled days is acceptable). The actual dose of cisplatin administered should be based on actual body surface area (BSA).

In case of obesity (body mass index (BMI) >30 kg/m²), actual BSA will still be used according to the ASCO recommendation published in the Journal of Clinical Oncology, 2012: Appropriate Chemotherapy Dosing for Obese Patients with Cancer (Appendix 8).

Cisplatin is to be given on a Q3W schedule of 100 mg/m² (a weekly dosing schedule is not allowed on protocol) on Day 1, 22 and 43 of the CRT phase. The 100 mg/m² dose may be split over 2 to 4 consecutive days (eg, 50 mg/m² on 2 consecutive days up to 25 mg/m² over 4 consecutive days) if that is the institutional standard way of delivering the Q3W cisplatin dosing. It is recognized that some patients will not be able to receive the 3rd dose of cisplatin and this is not a protocol deviation.

Complete information for cisplatin may be found in the SRSD, which for this study is the cisplatin package insert.[37]

5.4.2.1. Formulation

Each vial contains 10 mg of cis-diamminedichloridoplatinum, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 mL of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 19 mg sodium chloride (NaCl) and hydrogen chloride (HCl) or sodium hydroxide (NaOH) to adjust pH.

5.4.2.2. Administration

Cisplatin is highly emetogenic. After administering appropriate antiemetics (see Section 5.5.2.1), cisplatin will be infused over 60-120 minutes for the 100 mg/m^2 dose along with vigorous hydration per local standard of care. Please refer to the study Investigational Product (IP) manual for further details regarding cisplatin administration.

5.4.2.3. Storage and Stability

Please refer to the study IP manual for cisplatin storage and stability data.

5.4.2.4. Adverse Events

Refer to the cisplatin package insert for safety data.

5.4.2.5. Supply

Cisplatin is commercially available. The Sponsor will provide cisplatin to individual study sites as required. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 Code of Federal Regulations (CFR) 312.2(b) for Investigational New Drug (IND) exemption.

5.4.3. Avelumab/Placebo

5.4.3.1. Dosage Form and Packaging

Avelumab/placebo will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL with a nominal volume of 10 mL in glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each vial is intended for single-use only.

The placebo for avelumab is a sterile, clear, and colorless solution for IV administration presented with a nominal volume of 10 mL in matching glass vials. Each vial is intended for single-use only.

Packaging and labeling of avelumab/placebo will be blinded to all investigative personnel in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Avelumab/placebo will be packed in boxes each containing one vial. The information on the trial drug will be in accordance with approved submission documents.

Avelumab/placebo will be shipped in transport cool containers (2°C to 8°C) with temperature monitoring devices.

5.4.3.2. Preparation and Dispensing

Avelumab 10 mg/kg or placebo will be administered on Day 1 of the Lead-in Phase and Day 8, Day 25, and Day 39 of the CRT Phase after all procedures/assessments have been completed as described in the Schedule of Activities (excluding IMRT). Avelumab/placebo or cisplatin may be administered either before or after the RT fraction that is administered on the same day; however, it is preferred that administration of these agents occur prior to RT. See the dosage and administration instructions in the Investigational Product Manual for instructions on how to prepare the investigational products for administration. Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of study agents.

The contents of the avelumab/placebo vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products and should be documented in case report forms (CRFs).

For administration in this trial, avelumab/placebo drug product must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Investigational Product Manual. Tubing with in-line, low protein binding 0.2 micron filter made of polyether sulfone (PES) must be used during administration.

The dose amount required to prepare the avelumab/placebo infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every cycle. If the patient experienced a weight change of >10% compared to the weight that was used for the last dose calculation, the amount of study drug must be recalculated. It is at the site's discretion however, to recalculate the avelumab/placebo dose at weight changes below the threshold for mandatory recalculations.

Avelumab/placebo must not be used for any purpose other than the trial. The administration of trial drug to patients who have not been enrolled into the trial is not covered by the trial insurance.

Any unused portion of the avelumab/placebo solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

5.5. Administration

All study treatments (IMRT, cisplatin, and avelumab/placebo) will be administered at the investigational site on an outpatient basis.

Avelumab/placebo or cisplatin can be given either before or after the RT fraction that is given on the same day; however, it is preferred that administration of these agents occur prior to RT.

5.5.1. Avelumab/Placebo

On each of the days that avelumab/placebo is administered (see Schedule of Activities table for details), the investigational product will be administered after all procedures/assessments have been completed as described in the Schedule of Activities table.

In order to mitigate infusion-related reactions, premedication should be administered as described in Section 5.5.1.4. This may be modified based on local treatment standards and guidelines, as appropriate. When investigational product and IMRT are administered on the same day, premedication should be timed relative to the infusion.

Avelumab/placebo will be administered as a 1-hour infusion. Sites should make every effort to target the timing of avelumab/placebo infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes are permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 5.5.1.5.

Avelumab/placebo dose reduction for toxicity management is not permitted; however, the next administration may be omitted due to persisting toxicity as described in Table 5, Table 6, and Table 7. Patients experiencing toxicity may require treatment adjustment or discontinuation according to the guidelines specified in Table 5, Table 6, and Table 7. Laboratory draws may be performed and results reviewed by the treating physician up to 1 business day before study drug administration. Laboratory draws taken 1 business day prior to infusion will not be considered a deviation.

During the Maintenance Phase, avelumab/placebo may be administered up to 3 days before or after the scheduled treatment day of each cycle for administrative reasons, except for C1D1. Maintenance C1D1 is defined as the day when the first avelumab/placebo is given, therefore there is no window required as the delivery of this dose defines the beginning of maintenance, irrespective of when the infusion is given.

Patients will receive trial treatment until completion of treatment per protocol, disease progression (PD) per modified RECIST v1.1 (Appendix 3), unacceptable toxicity, withdrawal of consent, patient is lost to follow-up, or until the study is terminated by the Sponsor, whichever occurs first.

Patients who temporarily stop the study treatment(s) due to AE may resume treatments upon recovery as described in Table 5, Table 6, or Table 7.

5.5.1.1. Treatment After Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents such as avelumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression, assigned study treatment should be continued while awaiting pathological confirmation of disease progression per modified RECIST v1.1 unless the patient is clinically unstable and/or requires an urgent alternative intervention (eg, decompression of a spinal cord compression). All locoregional disease recurrence or progression must be pathologically confirmed (see Appendix 3).

If the patient has confirmed PD per modified RECIST v1.1 by investigator assessment, the patient should discontinue from investigational products.

5.5.1.2. Recommended Dose Modifications

Every effort should be made to administer the investigational products at the planned dose and schedule.

No dose modifications of avelumab/placebo are permitted in this study, but the next infusion may be omitted based on persisting toxicity, as outlined in the next sections.

5.5.1.3. Dosing Delays

In the event of significant toxicity, dosing for the investigational products may be delayed or modified as described below. In the event of multiple toxicities, dose delays should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom. In addition to dose delays, investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Each of the 3 treatment components (IMRT, cisplatin, and avelumab) can cause significant toxicities, some of which may be overlapping. Determining the main cause of a toxicity may rely on the temporal relationship of the event to one of the agents, specific characteristics or the likelihood of developing such a toxicity relative to patients receiving only that modality. Investigator judgment may be required to best determine which agent to hold or modify. Recommendations for the management of each agent's toxicity are addressed individually in the following sections.

Both cisplatin and avelumab/placebo will be delayed appropriately if the IMRT is delayed. All treatment days in the Schedule of Activities table for the CRT Phase are predicated on radiation treatment days and neither systemic agent should be delivered in the CRT Phase if radiation is being held for toxicity management.

In case treatment interruption for one of the investigational drugs (cisplatin or avelumab/placebo) is required for drug-related toxicity, the dose of the other drug may also be modified or interrupted based on the guidance provided for toxicity management, product labeling, and institutional guidelines according to investigator's best medical judgement.

5.5.1.3.1. Study Treatment Modifications for Avelumab/placebo Drug-Related Toxicity

Recommended avelumab/placebo treatment modifications in case of avelumab/placebo drug-related toxicity are shown in Table 5. These specific guidelines are applicable in cases which have a causality attributed to avelumab/placebo. In cases where it is possible that an AE is related to both study treatments (avelumab/placebo and CRT), the guidelines for avelumab/placebo should be followed.

Table 5. Treatment Modifications for Avelumab/placebo-Related Toxicity – to be followed only when the AE is deemed related to avelumab/placebo.

Toxicity	NCI CTCAE Severity Grade	Avelumab/placebo Treatment Modification
Avelumab/placebo General Toxicity Management (other than infusion-related reaction/ hypersensitivity and irAEs)	Grade 1	• Continue as per schedule.
	Grade 2	• Continue as per schedule.
	Grade 3	• Withhold avelumab/placebo until recovery to Grade ≤1. • Permanently discontinue avelumab/placebo if toxicity does not resolve to Grade ≤1 within 12 weeks of last administration or upon recurrence of the same Grade 3 ADR except for laboratory values out of normal range that do not have any clinical correlate.
	Grade 4	• Permanent discontinuation, **Exceptions are:** • Laboratory values out of normal range that do not have any clinical correlate.
Infusion-related Reaction	Grade 1-4	• See Section 5.5.1.5 and Table 6.
Hypersensitivity reactions	Grade 3-4	• See Section 5.5.1.6 .
Immune-related AE (irAE)	Grade 1-4	• See section 5.5.1.8 and Table 7
Tumor lysis syndrome	Grade 1-4	• See section 5.5.1.7 and Figure 5.

5.5.1.4. Special Precautions for Avelumab/placebo Administration

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab/placebo should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

In order to mitigate infusion-related reactions, patients have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Following avelumab/placebo infusions, patients must be observed for 30 minutes post infusion for potential infusion related reactions.

Infusion of avelumab/placebo will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. If an infusion/allergic reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Treatment recommendations for the management of infusion-related reactions, severe hypersensitivity reactions, and tumor lysis syndrome are outlined in Section 5.5.1.5, Section 5.5.1.6, and Section 5.5.1.7, respectively.

Investigators should also monitor patients closely for potential irAEs, which may become manifest at the earliest weeks of treatment. Immune-related adverse events include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, rash, nephritis and other immune-mediated reactions including eye disorders (uveitis, iritis), myositis, and myocarditis. Treatment recommendations for the management of irAEs are outlined in Section 5.5.1.8.

5.5.1.5. Management of Avelumab/placebo Infusion-Related Reactions

Avelumab/placebo infusion-related reactions may occur. Symptoms may include fever, chills, rigors, diaphoresis, and headache).

Treatment of the infusion-related reaction and modifications of the infusion rate and/or treatment interruption/discontinuation are mainly dependent upon severity, as indicated in Table 6.

Table 6. Treatment Modification for Symptoms of Avelumab/Placebo Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modifications
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the investigational product infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	• Stop investigational product infusion. • Resume infusion at 50% of previous rate* as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, 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 investigational product infusion immediately and disconnect bag infusion tubing from the patient. • Investigational product treatment must be permanently discontinued.

IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.
*If avelumab/placebo infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.

Additional Modifications for Patients with Grade 2 Avelumab/Placebo Infusion-Related Reactions: In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 6 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication.

5.5.1.6. Management of Avelumab/Placebo-related Severe Hypersensitivity Reactions and Flu-like Symptoms

Many mAb therapies can induce flu-like symptoms and hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis.

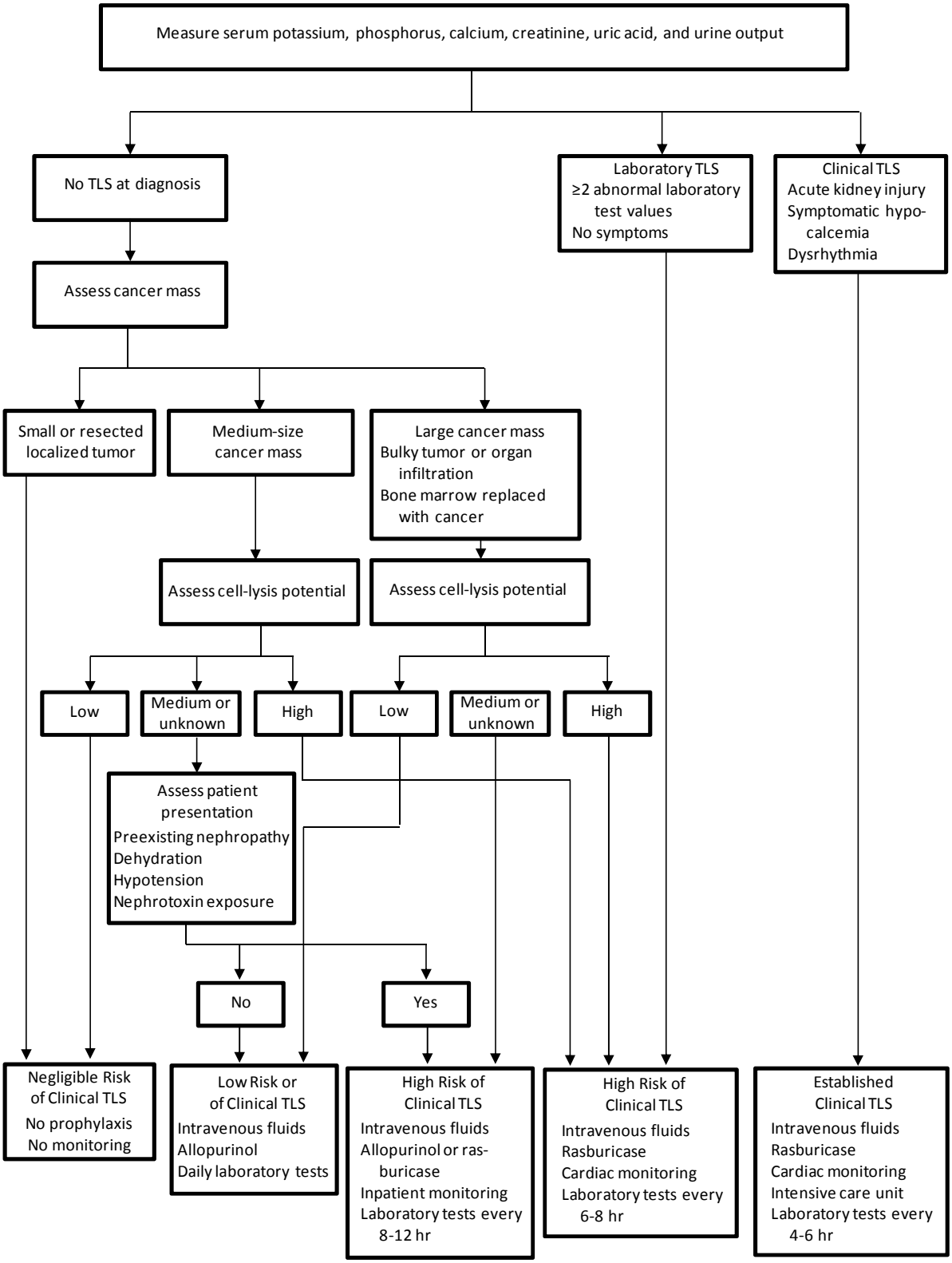
Avelumab/placebo should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment if required. Patient should be placed on monitor immediately and epinephrine injection and dexamethasone infusion should be available for immediate access.

For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable nonsteroidal anti- inflammatory drugs (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at Investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab/placebo IV infusion. Alternative treatments for fever (eg, paracetamol or ibuprofen) and rigors (eg, meperidine) may be given to patients at the discretion of the Investigator.

5.5.1.7. Management of Investigational Product-Related Tumor Lysis Syndrome

Avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), so there is a potential risk of tumor lysis syndrome. Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 5) published by Howard et al.[51]

Figure 5 Assessment and Initial Management of Tumor Lysis Syndrome (TLS)



5.5.1.8. Management of Avelumab/placebo Immune-Related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, avelumab/placebo may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (irAEs).

Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, rash, nephritis and renal dysfunction, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any AE which may have an underlying immune-mediated mechanism including those described above, and without other clear etiologies, should be considered immune-related and managed according to guidelines described in this section.

If a patient has an AE that may be considered immune mediated, treatment for the AE should be administered as if the patient is receiving avelumab.

Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v4.03):

- Grade 1 or 2: treat symptomatically or with moderate-dose steroids, more frequent monitoring;
- Grade 1 or 2 (persistent): manage similar to high grade AE (Grade 3 to 4);
- Grade 3 or 4: treat with high-dose corticosteroids.

Treatment of irAEs should follow guidelines set forth in Table 7.

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI CTCAE v4.03)	**Initial management**	**Follow-up management**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	• Continue avelumab/placebo therapy • Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3 or 4
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with activities of daily living (ADL) Colitis: abdominal pain; blood in stool	• Withhold avelumab/placebo therapy • Symptomatic treatment	If improves to Grade 1: • Resume avelumab/placebo therapy If persists >5-7 days or recur: • Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	• Withhold avelumab/placebo for Grade 3 • Permanently discontinue avelumab/placebo for Grade 4 or recurrent Grade 3 • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab/placebo therapy following steroids taper (for initial Grade 3) If worsens, persists >3 to 5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication); Note: infliximab should not be used in cases of perforation or sepsis

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

Dermatological irAEs		
Severity of Rash (NCI-CTCAE v4.03)	**Initial management**	**Follow-up management**
Grade 1 to 2 Covering ≤30% body surface area	• Symptomatic therapy (eg, antihistamines, topical steroids) • Continue avelumab/placebo therapy	If persists >1 to 2 weeks or recurs: • Consider skin biopsy • Withhold avelumab/placebo therapy • Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy following steroids taper. If worsens: • Treat as Grade 3 to 4
Grade 3 Covering >30% body surface area **Grade 4** Life-threatening consequences	• Withhold avelumab/placebo for Grade 3 • Permanently discontinue avelumab/placebo for Grade 4 or recurrent Grade 3 • Consider skin biopsy • Dermatology consult • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: • Taper steroids over at least 1 month • Resume avelumab/placebo therapy following steroids taper (for initial Grade 3)
Pulmonary AEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Initial management**	**Follow-up management**
Grade 1 Radiographic changes only	• Consider withholding avelumab/placebo therapy • Monitor for symptoms every 2 to 3 days • Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or Grade 3 to 4

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

Grade 2 Mild to moderate new symptoms	• Withhold avelumab/placebo therapy • Pulmonary and Infectious Disease consults • Monitor symptoms daily, consider hospitalization • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: • When symptoms return to Grade 1, taper steroids over at least 1 month and then resume avelumab/placebo therapy following steroids taper If not improving after 2 weeks or worsening: • Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	• Permanently discontinue avelumab/placebo therapy • Hospitalize • Pulmonary and Infectious Disease consults • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: • Taper steroids over at least 1 month. If not improving after 48 hours or worsening: • Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Liver Function Tests (LFT) Increase (NCI-CTCAE v4.03)	**Initial management**	**Follow-up management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	• Continue avelumab/placebo therapy	Continue liver function monitoring If worsens: • Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3x ULN	• Withhold avelumab/placebo therapy • Increase frequency of monitoring to every 3 days • Permanently discontinue investigational product therapy if AST/ALT >3X ULN with concurrent elevation if total bilirubin >2X ULN without another obvious cause	If returns to Grade ≤1: • Resume routine monitoring, resume avelumab/placebo therapy If elevations persist >5 to 7 days or worsen: • Treat as Grade 3 to 4

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	• Permanently discontinue avelumab/placebo therapy • Increase frequency of monitoring to every 1 to 2 days • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist/ hepatologist • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤1: • Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	**Initial management**	**Follow-up management**
Grade 1 **Creatinine increased > ULN to 1.5 x ULN**	• Continue avelumab/placebo therapy	• Continue renal function monitoring If worsens: • Treat as Grade 2 to 3 or 4
Grade 2 to 3 **Creatinine increased >1.5 and ≤6 x ULN**	• Withhold avelumab/placebo therapy • Increase frequency of monitoring to every 3 days • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy	If returns to Grade ≤1: • Taper steroids over at least 1 month, and resume avelumab/placebo therapy following steroids taper If worsens: • Treat as Grade 4
Grade 4 **Creatinine increased >6 x ULN**	• Permanently discontinue avelumab/placebo therapy • Monitor creatinine daily • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy • Nephrology consult	If returns to Grade ≤1: • Taper steroids over at least 1 month

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

Cardiac irAEs		
Myocarditis	**Initial management**	**Follow-up management**
New onset of cardiac signs or symptoms and/or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	• Withhold avelumab/placebo therapy • Hospitalize • In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management • Cardiology consult to establish etiology and rule-out immune-mediated myocarditis • Guideline based supportive treatment as per cardiology consult* • Consider myocardial biopsy if recommended per cardiology consult	• If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab/placebo therapy • If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis
Immune-mediated myocarditis	• Permanently discontinue avelumab/placebo • Guideline based supportive treatment as appropriate as per cardiology consult* • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections	• Once improving, taper steroids over at least 1 month • If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial management**	**Follow-up management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Continue avelumab/placebo therapy • Endocrinology consult if needed • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid	• Continue hormone replacement/suppression and monitoring of endocrine function as appropriate

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

	treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (ie, hypopituitarism/ hypophysitis)	
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Withhold avelumab/placebo therapy • Consider hospitalization • Endocrinology consult • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (ie hypopituitarism / hypophysitis)	• Resume avelumab/placebo once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression) • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab/placebo if	Resume avelumab/placebo once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement) In addition, for hypophysitis with abnormal MRI, resume avelumab/placebo only once shrinkage of the pituitary gland on MRI/CT scan is documented Continue hormone replacement/suppression therapy as appropriate

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

	mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab/placebo if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month • Add prophylactic antibiotics for opportunistic infections	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4.03)	**Initial management**	**Follow-up management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab/placebo therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab/placebo therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab/placebo therapy • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Specialty consult as appropriate	If improves to Grade ≤1: • Taper steroids over at least 1 month and resume avelumab/placebo therapy following steroids taper.
Recurrence of same Grade 3 irAEs	• Permanently discontinue avelumab/placebo therapy • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Specialty consult as appropriate	If improves to Grade ≤1: • Taper steroids over at least 1 month.
Grade 4	• Permanently discontinue avelumab/placebo therapy • 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed	If improves to Grade 1: • Taper steroids over at least 1 month

Table 7. Management of Avelumab/placebo Immune-Related Adverse Events – to be followed only when the Adverse Event is deemed immune related

	• Add prophylactic antibiotics for opportunistic infections • Specialty consult	
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	• Permanently discontinue avelumab/placebo therapy • Specialty consult	

ACTH=adrenocorticotropic hormone, ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BNP=B type natriuretic peptide, CK-MB=creatine kinase MB, CT=computed tomography, FSH=follicle stimulating hormone, GH=growth hormone, IGF-1=insulin-like growth factor 1, irAE=immune-related adverse event, IV=intravenous, LH=luteinizing hormone, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PRL=prolactin, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

5.5.2. Cisplatin

Cisplatin 100 mg/m^2 will be administered in 500 mL normal saline over a 60 – 120 minute infusion with an additional 1 to 1.5 L of fluid give post-hydration. Efforts should be made to dose cisplatin on Mondays or Tuesdays to maximize overlap with radiation therapy. See the IP manual for further details regarding cisplatin administration.

5.5.2.1. Management of Cisplatin Toxicities and Pretreatment Guidelines

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional or ASCO guidelines for highly emetogenic regimens should be followed. In the absence of such guidelines the following may be used:

- For acute nausea and vomiting, premedication should include a 5-HT3 (5-hydroxytryptamine 3) antagonist, such as granisetron 1 mg IV; ondansetron, up to to 16 mg IV; or palonosetron, 0.25 mg IV; plus a corticosteroid, such as dexamethasone, up to 20 mg IV. Palonosetron has a longer half life (40h) than the first generation 5HT3 antagonists.

- Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone. Potential delayed nausea regimens include:

    - The neurokinin (NK)-1 antagonist, may be added for prevention of delayed emesis on the day of cisplatin administration and for two consecutive days

thereafter (80, 80), with a corticosteroid, such as dexamethasone on Days 1-4. Dexamethasone should be reduced on Day 1 to 12 mg and delivered at up to 8 mg total daily for the 3 days following cisplatin administration. A 5HT3 antagonist (eg, granisetron, ondansetron) may be also given for the 3 days following cisplatin administration, only if palonosetron was not given prior to chemotherapy.

- Delayed emesis also may be managed by the addition of dexamethasone 8 mg administered twice daily (BID) x 2 days, followed by dexamethasone 4 mg BID x 2 days, beginning on the day after chemotherapy; and oral metoclopramide 0.5 mg/kg (usually 20-40 mg) four times daily (QID) x 2-4 days. A 5HT3 antagonist (eg, granisetron, ondansetron) may also be given for up to 3 days after cisplatin administration, only if palonosetron was not given prior to chemotherapy.

Patients must receive vigorous hydration and diuresis. A suggested regimen is prehydration with a 1 liter of D5NS (potassium chloride in 5% dextrose and sodium chloride) over 2-4 hours and mannitol, 12.5 g IV bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m^2, in 500-1000 mL normal saline (NS) is administered over 1-2 hours followed by an additional 1 to 1.5 liters of fluid. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management.

Additional IV hydration and blood urea nitrogen (BUN)/creatinine check also should be considered, if necessary, later in the week after cisplatin administration, in order to address any dehydration or severe fluid/electrolyte imbalance. On the second and third day following cisplatin, patients should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS.

5.5.2.2. Cisplatin Dose Modifications for Toxicity During Concurrent Radiation

Patients will be examined and graded for subjective/objective evidence of toxicity while receiving concurrent cisplatin with radiotherapy.

Chemotherapy dosage modifications are based upon laboratory values obtained within the 24 hours prior to cisplatin and non-hematologic toxicities during the week prior to a particular cisplatin dose. Laboratory draws can be performed 1 business day prior to cisplatin infusion ie, laboratory draws on Friday can be used for infusion on Monday providing that any abnormality compromising cisplatin infusion (eg neutropenia, creatinine increase) is re-assessed on the day of infusion.

The dose modifications for cisplatin (below) are intended to be permanent (ie, if the patient's dose is reduced to dose level -1, it remains at the reduced dose level for the remainder of the CRT Phase). There will be no dose re-escalation for cisplatin.

The dose of cisplatin may be modified on Days 22 and/or 43 for the following toxicities:

Table 8. Cisplatin Dose Levels

Cisplatin Starting Dose	Dose Level -1	Dose Level -2
100 mg/m^2	75 mg/m^2	50 mg/m^2

5.5.2.2.1. Cisplatin-Related Hematologic Adverse Events

Chemotherapy must not be administered until the patient's ANC is ≥1,000/mm^3 and platelets are ≥75,000/mm^3. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

Table 9. Cisplatin Dose Modifications Due to Hematological Toxicity

ANC		Platelets	Reduction
≥1000/mm^3		≥75,000/mm^3	None
<1000/mm^3	or	<75,000/mm^3	One dose level

If on Day 22, neutropenia or thrombocytopenia prevents administration of cisplatin, but there is no contraindication for avelumab/placebo, then avelumab/placebo may be given on Day 22 and cisplatin on any day between Days 25 to 33 if ANC and platelet counts recover. If avelumab/placebo is administered on Day 22, then the following dose of avelumab/placebo should then be administered 14 days later on Day 36. The Day 43 dose of cisplatin can be given any time up to 5 days after the end of radiation therapy.

5.5.2.2.2. Cisplatin-Related Non-Hematologic Adverse Events

Neutropenic Fever

Temperature of 38.5°C with ANC <1000/mm^3 is an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever is encountered, then the chemotherapy dose reduction will be determined by the weekly blood counts (see Table 9).

Renal Toxicity

Cisplatin dose should be based on the serum creatinine or creatinine clearance immediately prior to the second cisplatin dose using the following guidelines. Note: If creatinine is >1.5 mg/dL, creatine clearance must be calculated (Cockcroft-Gault) in order to make a dose adjustment. If the calculated clearance is ≥50 mL/min, a 24-hour urine collection is not needed. However, if the calculation is <50 mL/min, a 24-hour urine collection is required, and the cisplatin dose will be determined as described in Table 10.

Table 10. Cisplatin Dose Modification Due to Decreased Creatinine Clearance

Serum Creatinine		Creatinine Clearance	Cisplatin Dose
≤1.5 mg/dL	OR	>50 mL/min	100 mg/m^2
>1.5 mg/dL	AND	40-50 mL/min	50 mg/m^2
>1.5 mg/dL	AND	< 40 mL/min	Hold cisplatin[a]

a. Cisplatin should be held (but the RT continued) and the creatinine measured weekly, until it is <1.5 mg/dL or the creatinine clearance is >50 mL/min, and then the second dose of cisplatin should be given at the reduced dose of 50 mg/m^2.

Neurologic (Neuropathy) Adverse Events:

Table 11. Cisplatin Dose Modifications Due to Neurologic Toxicity

CTCAE Grade	Dose Reduction
0 – 1	None
2	One dose level
3 – 4	Hold drug

Ototoxicity:

Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale, including the CTCAE, v4.03, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (>Grade 2) hearing loss. However, for clinical Grade 3 or higher hearing loss, cisplatin should be held and for Grade 2 clinical hearing loss, one dose level reduction.

Dependent upon the requirements documented in each country's cisplatin SmPC, patients may require a baseline audiogram and a second audiogram within 12 weeks after the completion of CRT to monitor for potential ototoxicity related to cisplatin administration. Audiograms are a requirement in France. For other countries that may have this requirement for cisplatin administration, refer to the local cisplatin SmPC.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation:

For Grade>2 toxicities (excluding lymphopenia, mucositis, or dysphagia), hold cisplatin, re-evaluate weekly until AE resolves to Grade ≤1, then restart cisplatin at one lower dose level.

5.5.2.3. Cisplatin Dosing Delays

Cisplatin chemotherapy will be delayed appropriately if treatment course is delayed (ie, second and third courses are administered on the 22nd and 43rd day of radiation therapy. If the second dose of cisplatin is delayed more than 21 days because of hematologic, neurologic, renal, or other adverse events, that dose will be omitted.

If the Day 22 dose of cisplatin cannot be administered due to toxicity, but there is no contraindication for avelumab/placebo, avelumab/placebo may then be given on Day 22 and cisplatin administered on any day between Day 25 to 33 if the toxicity resolves. If avelumab/placebo is administered on Day 22, the following dose of avelumab/placebo should then be administered 14 days later on Day 36. The Day 43 dose of cisplatin can be given any time up to 5 days after the end of radiation therapy.

It is expected that approximately 30% of patients will not be able to receive the 3rd dose of cisplatin due to related toxicity and this is not a PD.

5.5.2.4. Concurrent Radiation Therapy Adverse Events

Grade 3 or 4 (CTCAE v4.03) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (eg, greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis.

Much less common radiation adverse events include: mandibular osteoradionecrosis (<5% incidence), and cervical myelopathy (<1% with restriction of spinal cord dose to ≤45 Gy).

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy-attributable AEs requiring a break in treatment, IMRT may continue if clinically appropriate.

5.5.3. Food Requirements

All investigational products may be administered without regard to food.

5.6. Investigational Product Storage

The Investigator, or an approved representative, eg, pharmacist, will ensure that avelumab/placebo and cisplatin are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Avelumab/placebo and cisplatin should be stored in its original container and in accordance with the label. See the Investigational Product (IP) Manual for storage conditions of the avelumab/placebo product once diluted. Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C (80.6)°F and should be protected from light if not used within 6 hours. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Both avelumab and placebo must be stored in the refrigerator at 2° - 8°C (36° - 46°F). Do not freeze. Protect from light. Do not shake vigorously.

Storage conditions stated in the SRSD (IB)[17] for avelumab and SRSD for cisplatin (package insert)[37] will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the investigational products are briefly out of the temperature range described in the labeling are not considered excursions. More specific details will be provided to the sites separately.

All study drug supplies must be kept in a locked, limited access room. Avelumab/placebo must not be used outside the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor. The Investigator and or site staff must report any unacceptable condition of the investigational product to the site monitor.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

Pfizer may supply drug accountability forms that must be used or may approve of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient by patient basis, including specific dates and quantities.

The prescribed dose must be recorded in the patient's medical records. Drug dispensing needs to be verified and documented by a second individual and the forms must be signed by both the individual who dispensed the drug and the second individual who verified the dispensing. Copies must be provided to Pfizer.

5.7.1. Destruction of Investigational Product Supplies

At the end of the trial, or at appropriate points during the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented. If drug destruction is not permitted locally, Pfizer should be contacted for further directions.

5.8. Concomitant Treatment(s)

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines (for example, the influenza vaccine).

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy may be required. The Investigator should consult with the Sponsor about individual cases. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the investigator, the Sponsor, and the patient.

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment or until the start of new therapy, whichever comes first. All concomitant medications and non-drug supportive interventions should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis, infusion reaction prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Recommended medications to treat infusion-related reactions, hypersensitivity reactions and flu-like symptoms, tumor lysis syndrome and immune-related events are reported in Section 5.5.1.5, Section 5.5.1.6, Section 5.5.1.7, and Section 5.5.1.8, respectively.

5.8.1. Hematopoietic Growth Factors

The use of Erythropoietin is prohibited during radiation therapy.

Hematological toxicity related to cisplatin should follow the modifications as stipulated in Table 9 of the protocol which states that for ANC <1000/mm³ or platelets <75.000/mm³ the infusion should be held until recovery and the next dose should be one level down (75 mg/mm³).

According to ASCO guidelines (Journal of Clinical oncology (JCO) 2012),[63] colony stimulating factors (CSF) should not be routinely used for afebrile neutropenia and secondary prophylaxis should be recommended in case dose reduction or treatment delay may compromise treatment outcome.

If the investigator deems the administration of CSF warranted, its use may be allowed after consultation with, and approval by, the Sponsor.

5.8.2. Concomitant Surgery

5.8.2.1. Primary treatment neck dissection

Neck dissections within 20 weeks (140 days) of the completion of CRT are considered part of the initial treatment plan as defined in Appendix 3.

5.8.2.2. Other Surgery

In case of a surgical procedure, study treatment should be delayed. If a surgical requirement is required during the CRT Phase, CRT administration is to be held until patient recovery, at which time investigator assessment of the appropriateness of continuing definitive CRT is required for study treatment re-initiation. Re-initiation at any phase of study treatment should be discussed with the Sponsor.

5.8.3. Other Prohibited Concomitant Medications and Treatments

Patients are prohibited from receiving the following therapies during the treatment (CRT and Maintenance) phases of this trial:

- Anti-cancer systemic chemotherapy or biological therapy or investigational agents other than avelumab.
- Immunotherapy not specified in this protocol.

- Immunosuppressive drugs (ie, systemic corticosteroids or other immunosuppressants except for short term treatment of allergic reactions, toxicity management associated with cisplatin, or for the treatment of irAEs). Topical and inhalation steroids are allowed.

- Medications or vaccinations specifically prohibited in the exclusion criteria.

- Any vaccine therapies for the prevention of infectious disease within 4 weeks of start of study treatment, except administration of the inactivated vaccine.

- Bisphosphonate or denosumab treatment unless it has been initiated more than 14 days prior to receiving the first administration of avelumab.

- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).

- Vitamins used as anticancer treatments.

Clarifications About Steroid Use with Avelumab: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[52,53] Furthermore, as with all immunotherapies intended to augment cell mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 compounds indicate that short term use of steroids may be employed without compromising clinical outcomes.[54] Therefore, the use of steroids during this trial is restricted as follows:

Therapeutic use: for the treatment of infusion-related reactions and short term treatment of irAEs, steroids are permitted according to the modalities indicated in Section 5.5.1.8.

- Steroid administration required for cisplatin administration should be completed per institutional practice.

- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

- Prophylactic use, eg, prophylactic use prior to CT or MRI.

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

5.9. Rescue Medications and Supportive Care

5.9.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. See also ASCO guidelines for treatment of nausea and vomiting.[56]

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 5.

- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time (PT)/international normalized ratio (INR) should be performed.

5.10. Potential for Drug-Drug Interactions with Cisplatin

Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.

Cisplatin might reduce the absorption of phenytoin thereby leading to reduced control of epilepsy. Per country's product labeling, anti-seizure medication might have to be changed to an alternative that is not contra-indicated with cisplatin administration.

In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.[37]

6. STUDY PROCEDURES

All patients must sign an informed consent prior to any study-specific procedures.

All assessments should be performed prior to dosing with IV study treatments unless otherwise indicated on the Schedule of Activities table. Assessments can be performed before or after daily IMRT during the CRT Phase. Acceptable time windows for performing each assessment are described in the column headers on the Schedule of Activities table where applicable.

6.1. Screening

For screening procedures, see Schedule of Activities table as well as the Assessments section (Section 7).

Following informed consent, patients who complete screening assessments and are determined to be eligible may be registered use the IRT system. Screening assessments for eligibility MUST have already been completed before the patient is enrolled. To allow for additional flexibility in scheduling patient visit and procedures, Screening and Lead-in Day 1 procedures may be completed on the same day (see Schedule of Activities table).

6.2. Study Treatment Period

For all on-treatment activities, see Schedule of Activities table as well as the Assessments section (Section 7).

6.2.1. Tumor Biospecimens

6.2.1.1. Mandatory Tumor Tissue

An archival FFPE tumor tissue block from the most recent tumor resection or biopsy must be provided for all patients enrolled in the study and submitted to the Central Laboratory prior to randomization. If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable. Tumor tissue from cytologic sampling (eg, fine-needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.

6.2.1.2. Optional Tumor Tissue – Lead-In Phase

An optional tumor biopsy, to be collected 4 to 7 days following the single dose of avelumab in the Lead-in Phase, is requested for analysis of potential biomarkers of response. The de novo biopsy should be FFPE as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory.

6.2.1.3. De Novo Tumor Tissue – Maintenance Phase

For patients who, during the course of the study, undergo a clinically-indicated tumor resection procedure, a tumor sample from the procedure should be collected and submitted to the Central Laboratory as an FFPE tissue block.

6.2.1.4. De Novo Tumor Tissue – End of Treatment/Withdrawal

A de novo (ie, fresh biopsy) tumor sample should also be collected at the End of Treatment/Withdrawal visit, unless clinically contraindicated or no tumor remains.

Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted. The de novo biopsy should be FFPE as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory.

6.3. End of Treatment, Short- and Long-term Follow-up Visits

For End of Treatment, Follow-up, and Long-term Survival procedures, see Schedule of Activities table as well as Assessments section (Section 7).

In patients receiving investigational product up to the time of End of Treatment visit, additional safety follow-up visit will be scheduled for 30 days after the last dose received (Day 30 ± 3) and a follow-up phone call will be performed 90 days after the last dose received (Day 90 ± 3 [telephone contact]). If any concern arises during the follow-up phone call, the patient will be called in for a follow-up visit within 5 calendar days of the initial phone call for appropriate assessment (as per the investigator's medical judgement).

Patients continuing to experience treatment related toxicity following discontinuation of study treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

6.4. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Disease progression per modified RECIST v1.1;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is clearly attributed to one of the investigational products, then withdrawal from study treatment may be considered, dependent upon the treatment and specific toxicity. If a patient cannot tolerate cisplatin, or has a toxicity-related treatment delay due to the radiation therapy, withdrawal from this study is neither required nor suggested;
- Pregnancy;
- Significant protocol violation (including radiation therapy protocol violations);
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Study terminated by the Sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Assessment of Progression

For all suspected progression of disease that is detected clinically, but is not visible on radiographic imaging, direct imaging (ie, photographs) are required. This requirement is in addition to the requirement for pathologic confirmation of progression.

Tissue (pathologic) confirmation of disease is expected and required on this protocol for all local and regional lymph node suspected progression of disease. It is highly recommended that all new distant lesions suspicious for metastatic disease are also biopsied and pathologically confirmed. Good clinical judgment is expected to be utilized on biopsy ascertainment including, but not limited to, the situations below.

The following are expectations for biopsy ascertainment on a patient. If any of these conditions are met, it is expected that a biopsy will be performed, and the reason for biopsy and pathologic findings noted in the CRF. If a biopsy is not performed, clinical rationale must be entered into the CRF.

- New or significantly increased lesions on imaging or clinical exam;
- Mucosal ulceration;
- Suspicious mucosal changes;
- Suspicion of unresolved disease at the primary tumor location at the 12 week post CRT visit (primary treatment failure and a PD event if biopsy is positive);
- Significant enlargement, or newly enlarged, regional lymph nodes on clinical exam or imaging;
- Areas of PET-positive fludeoxyglucose (FDG)- uptake;
- Change of clinical findings on regional lymph node (neck) exam with new enlargement of a lymph node or group of nodes, or changes in character of lymph node group to palpation (eg, becoming harder or decreased mobility on physical exam - such as feeling attached to overlying skin, subcutaneous tissue or muscles, or underlying bone or muscle).

7.2. Safety Assessments

Safety assessments will include collection of AEs, Serious Adverse Events (SAEs), vital signs, physical examination, electrocardiogram (ECG, 12-lead), and laboratory assessments (including pregnancy tests). Further details of these assessments are described in the Schedule of Activities table.

7.2.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL human chorionic gonadotropin (hCG) and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment - once at the start of screening and once at Day 1 of the Lead –in Phase, immediately before administration of avelumab/placebo. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy result will then be required at Day 1 of the Lead-in Phase visit before the patient may receive the study treatment. Pregnancy tests (serum or urine) will also be routinely repeated as described in the Schedule of Activities prior to each dose of study treatment during the active treatment period, at the End of Treatment visit, during the post-treatment safety follow-up visits up to at least 30 days after the last study treatment infusion, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of study treatment but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (EC) or if required by local regulations.

7.2.2. Adverse Events

Assessment of adverse events will include the type and severity (graded by NCI CTCAE version 4.03), timing, seriousness, and relatedness. Adverse events that occur during the study will be recorded on the adverse events CRF page.

Baseline signs and symptoms should be recorded in the medical history CRF page.

7.2.3. Laboratory Safety Assessments

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the Schedule of Activities and analyzed at local laboratories. They may also be performed when clinically indicated. Abnormal laboratory test results should be repeated as soon as possible (preferably within 24-48 hours). The required laboratory tests are listed in Table 12.

Table 12. Required Laboratory Tests

Hematology	Chemistry Panel (*denotes core chemistry test)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT*	Protein, glucose, blood	PT or INR	For female patients of childbearing potential, serum or urine
Platelets	AST*		aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Total Calcium*			
	Total Bilirubin* °			
	BUN or Urea*			
	Creatinine*			
	Glucose*			
	Phosphorus or Phosphate*			
	Albumin*			
	Total Protein*			
	Uric Acid			
	Amylase			
	Gamma glutamyl transferase (GGT)			
	Cholesterol			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			
	Lipase			
	Triglycerides			
	HBV, HCV serology			
	Thyroid Function Tests: TSH, free T4			
	Other Tests: ACTH,			

° For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, PT/INR, alkaline phosphatase, and acetaminophen levels.

ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PT=prothrombin time, TSH=thyroid-stimulating hormone, WBC=white blood cell

7.2.4. Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, assessment of ECOG performance status, weight and height (height will be measured at screening only) at the time points described in the Schedule of Activities table.

At baseline evaluation, nasopharyngoscopy is strongly recommended.

Weight for the purposes of dose calculation will be recorded at screening and within 3 days prior to each dose of avelumab. Baseline weight is used for the Lead-in D1 dose calculation.

Vital signs (blood pressure and pulse rate) will be also recorded as reported in the Schedule of Activities table. They should be taken before any other assessments (eg, PK, laboratory blood draws), prior to receipt of study treatment with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

7.2.5. 12-Lead Electrocardiograms

All patients require a single ECG measurement at screening and at the End-of-Treatment/Withdrawal visit or when clinically indicated. Clinically significant findings seen on ECG during the treatment period should be recorded as adverse events.

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be collected in approximately 30 patients in each arm of the study. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. In these patients, on-treatment triplicate ECGs will be performed on the day of avelumab/placebo administration (ie, Day 1 of the Lead-in Phase, and Days 8, 25, and 39 of the CRT Phase; if the avelumab/placebo dosing day is shifted for patient scheduling reasons, the ECG assessment should be shifted also). At each time point (see the Schedule of Activities) 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates) prior to avelumab/placebo administration and at the end of infusion. If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate.

If a manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring as clinically indicated. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to ≤500 msec. Patients will then restart the investigational product at the next lowest dose level or have their dosing delayed as appropriate for specific investigational product. If the QTc interval has still not decreased to <500 msec after 2-weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of prolongation of the QTc interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist.

If a patient experiences any cardiac or neurologic AEs (especially syncope, dizziness, seizures, or stroke), an ECG in triplicate should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

Clinically significant findings seen on ECGs during the treatment period should be recorded as AEs.

7.3. Pharmacokinetics Assessments

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. If a scheduled blood sample collection cannot be completed for any reason, the missed sample may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

- As part of understanding the pharmacokinetics of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.3.1. Blood for PK Analysis of Avelumab

Blood samples (3.5 mL whole blood) for PK analysis of avelumab will be collected in all patients into an appropriately labeled serum separator tube (SST) as outlined in the Schedule of Activities table. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.3.2. Blood for PK Analysis of Cisplatin

Blood samples (5 mL whole blood at each time point) will be collected for PK analysis of cisplatin in a total of 24 patients (12 patients in Arm A and 12 patients in Arm B) at selected sites into appropriately labeled tubes as outlined in the Schedule of Activities table. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.4. Immunogenicity Assessments

The sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA may be further analyzed for neutralizing antibodies (nAb).

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial in the Study Manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.
- As part of understanding the immunogenicity of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.4.1. Immunogenicity Assessment of Avelumab

Blood samples (3.5 mL whole blood) will be collected for development of avelumab ADAs into an appropriately labeled SST. This monitoring will take place at regular intervals during the treatment and follow-up periods as described in the Schedule of Activities table. All samples that are positive for ADA may also undergo characterization for Nab.

7.5. Translational and Pharmacodynamic Assesments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may identify those patients who benefit from treatment with the combination of avelumab and CRT. In addition, analyses of sequentially obtained blood biomarkers will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment/Withdrawal visit will also help understand potential acquired mechanisms of resistance to the drug combination.

7.5.1. Tumor Biospecimens

Tumor biospecimens representing tissue samples from tumor resection or biopsy (see Section 6.2.1) will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Markers that may be analyzed include but may not necessarily be limited to: PD-L1 expression and tumor infiltrating CD8+ T lymphocytes by IHC; and/or tissue expression of FoxP3, PD-1, PD-L2; homologous recombination deficiency testing on tumor tissue. Samples obtained during the Lead-in Phase (optional), Maintenance Phase (in patients who undergo a clinically-indicated tumor resection), and/or at the End of Treatment/Withdrawal visit (all patients) will be assessed in parallel with the mandatory pre-treatment biospecimens(s) to provide data on the changes in the tumor that accumulated over the course of therapy, including acquired mechanisms of resistance. Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable. Tumor tissue collected (via slides) in China will not be retained and will be examined for PD-L1 expression and CD8 lymphocyte infiltration by immunochemistry, tumor mutational burden and immune repertoire by T-cell receptor (TCR) analysis.

Additional information on tissue collection procedures can be found in the Study Manual.

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[redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

7.7. Patient-Reported Outcomes Assessments

The NCCN FHNSI-22 (Appendix 6), EQ-5D-5L (Appendix 7), CCI [redacted] will be administered at time points described in the Schedule of Activities in the clinic by the patient. These questionnaires cannot be taken home. CCI [redacted]

7.8. Tumor Response Assessment

Tumor assessments will include all known or suspected disease sites. Imaging at screening (baseline) and at 12 weeks after completion of CRT must include a head and neck CT or MRI, chest CT, and PET scan. High resolution PET/CT does not require additional CT thorax/neck/brain. MRI brain may be performed if clinically indicated. Other areas may be scanned as clinically indicated. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. At a minimum, the CT modality used at baseline will be the expected imaging technique for follow-up. Any clinical progression concern warranting a biopsy must have supporting imaging (ie, CT, MRI, PET, or digital photograph) archived for documentation purposes. Additional imaging modalities may also be employed if clinically required. Baseline tumor assessments should be done within 28 days prior to randomization.

Radiographic and clinical evaluations will be conducted with the same schedule in both treatment arms of the study. The investigator will assess antitumor activity based on radiological assessments and clinical evaluation of patients using modified RECIST v1.1 (Appendix 3) at screening (baseline), 12 weeks after the completion of CRT, every 16 weeks thereafter for 48 months (208 weeks), and every 24 weeks (Q24W) thereafter until confirmed disease progression per modified RECIST v1.1 and regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy.

The assessment performed 12 weeks after completion of the CRT is to include CT and PET for all patients and MRI also if clinically appropriate in patients who did not achieve clinical or CT/MRI-based radiological nodal CR at the tumor assessment performed 12 weeks following completion of CRT, and follow-up PET scans are recommend every 4 months (16 weeks) with the CT imaging for 24 months (104 weeks), then every 6 months (Q24W) in Years 3-5. CT imaging should be obtained as described in the Schedule of Activities beyond Year 5. The time window for tumor assessments is ±1 week except for the assessment at Week 12 which cannot be done earlier but can be done up to one week later.

Additional radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or physical exam findings suggestive of mucosal recurrence). See the Schedule of Activities.

If radiologic imaging shows progressive disease, assigned study treatment should be continued while awaiting pathologic confirmation of disease progression per modified RECIST v1.1 unless the patient is clinically unstable and/or requires an urgent alternative intervention (eg, decompression of a spinal cord compression). All locoregional disease recurrence or progression must be pathologically confirmed (see Appendix 3). The date of progression will be the date of the radiographic evaluation that showed progression which was subsequently confirmed by pathology.

All radiographic images will be collected and stored for possible future objective verification by an independent third-party core imaging laboratory (central review) as described in the Study Manual. In addition any photographs of clinical progression concerns warranting biopsy will also be collected for potential future review.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through 90 days after last administration of investigational product.

- If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

The guidance on reporting of medication errors also applies to the reporting of overdose.

For purposes of this study, an overdose of avelumab or cisplatin is defined as any dose ≥5% over the calculated dose for that particular administration. Radiation dosing parameters are defined and limited in the Radiation Delivery Guidelines document.

There is no specific treatment for avelumab overdose. In the event of overdose with avelumab, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided as clinically indicated.

An acute overdose of cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of an overdosage of cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of cisplatin to proteins.

Treatment in the event of an overdose consists of general support measures.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section 8.8 on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with:

- For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;

- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

AEs will be reported using concise medical terminology (verbatim) as well as the grade from the CTCAE Version 4.03, http://ctep.cancer.gov/reporting.ctc.html) listed in the Cancer Therapy Evaluation Program.

If required on the AE CRFs, the investigator will use the following definitions of severity in accordance with CTCAE Version 4.03 to describe the maximum intensity of the adverse event (Appendix 5).

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

For combination study treatment, causality assessment will be performed for each of the individual drugs in the combination.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient/ legally acceptable representative. In addition, each study patient/ legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

This section describes the data analysis and statistical methods for this study.

9.1. Sample Size Determination

The study is designed to test the following hypotheses:

H_0: $HR_{PFS}(A/B) \geq 1$ *versus* H_a: $HR_{PFS}(A/B) < 1$

Where $HR_{PFS}(A/B)$ represents the hazard ratio (HR) for PFS in Arm A vs Arm B. A stratified log-rank test stratified by randomization stratification factors will be used for analysis of PFS.

Two hundred eighty-nine (289) PFS events will be required to have at least 90% power to detect a hazard ratio of 0.68 using a1-sided log-rank test at a significance level of 0.025, and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-7) β-spending function to determine the non-binding futility boundary.

The sample size of 640 patients for this study is determined based on the assumptions that the median PFS for patients in Arm B is 33 months[43,44] and that combination treatment including avelumab (Arm A) is expected to increase the median PFS to ≥48.5 months, corresponding to a HR of ≤0.68 under the exponential model assumption.

The sample size further assumes a 15% drop-out rate within each treatment arm and a non-uniform patient accrual over a 22-month period. The data cutoff for the primary PFS analysis will occur after the target number of events has been reached and the last patient randomized in the study has been followed for at least 24 months after randomization.

The sample size of 640 patients will also allow the assessment of a difference in OS. OS will be tested using a hierarchical testing procedure, provided the primary endpoint, PFS, is statistically significant favoring Arm A. A total of 392 OS events will be required to have 80% power to detect a HR of 0.75 using a 1-sided log-rank test at a significance level of 0.025 and a 5-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. It is assumed that the median OS for patients in Arm B is 70 months,[43,44] and that treatment with avelumab (Arm A) is expected to increase the median OS to ≥93 months, corresponding to a HR of ≤0.75 under the exponential model assumption. The sample size further assumes a 5% drop-out rate for OS in each treatment arm, and a follow-up of approximately 106 months after the last patient is randomized. The data cutoff for the final OS analysis will occur after the target number of deaths has been reached in the study.

9.2. Analysis Populations

9.2.1. Full Analysis Set

The full analysis set (FAS) will include all patients who are randomized. Patients will be classified according to the treatment assigned at randomization. The FAS will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.2.2. Per-Protocol Analysis Set

The per-protocol analysis set is a subset of the FAS and will include patients who do not meet criteria that could impact the key objectives of the study. These criteria will be pre-specified in the statistical analysis plan. The per-protocol analysis set will be used for sensitivity analyses of the primary efficacy endpoint, PFS.

9.2.3. Safety Analysis Set

The safety analysis set will include all patients who receive any study treatment. Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the treatment period, in which case patients will be classified according to the first treatment received. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

9.2.4. Pharmacokinetics Analysis Set

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least 1 concentration above the lower limit of quantitation (LLQ) for avelumab or cisplatin (total and free).

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least 1 of the PK parameters of interest for avelumab or cisplatin.

9.2.5. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least 1 ADA/Nab sample collected for avelumab in Arm A.

9.2.6. Biomarker Analysis Set

The biomarker analysis set is a subset of the safety analysis set and will include patients who have at least 1 screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

9.3. Efficacy Analysis

All analyses will be performed on the FAS unless otherwise specified.

All analyses will be performed by using SAS® Version 9.1.3 or higher.

9.3.1. Analysis of the Primary Endpoint

PFS is defined as the time from the date of randomization to the date of the first documentation of objective PD per modified RECIST v1.1or death due to any cause, whichever occurs first.

The following will be considered events in the analysis of PFS:

- Death due to any cause;

- Locoregional disease progression per RECIST v1.1 which is subsequently confirmed by pathology;
- Locoregional clinically detectable progression that is confirmed by pathology;
- Surgical removal (salvage) of primary tumor with tumor present on final pathology;
- Salvage neck dissection >20 weeks (140 days) after completion of SOC CRT with tumor present on final pathology;
- Metastatic (distant metastases) disease progression per RECIST v1.1.

For the primary analysis, PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD per modified RECIST v1.1 or death); the analysis will consider any PD per modified RECIST v1.1 or death as an event regardless of the number of prior missing tumor assessments or timing of the event with respect to initiation of anti-cancer therapy.

The primary analysis of PFS will be performed based on the FAS. A stratified log-rank test (1-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses with the overall significance level preserved at 0.025 (1-sided). PFS times associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported. The stratified Cox proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding 95% CI.

A sensitivity analysis for PFS will be performed using the methodology outlined for the primary analysis of PFS above but defining PD as per standard RECIST v1.1. Summary of discordance of PD (event and timing) as well as reasons for discordance between assessment of PFS per modified RECIST v1.1 and standard RECIST v1.1 will be provided for each treatment arm.

PFS based on modified RECIST v1.1 will also be evaluated based on the per-protocol analysis set as a sensitivity analysis using the methodology outlined for the primary analysis of PFS.

Other sensitivity analyses will be pre-specified in the SAP.

9.3.2. Analysis of Secondary Endpoints

9.3.2.1. Overall Survival

OS is defined as the time from date of randomization to date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, is statistically significant at the PFS interim or final analyses. In addition, OS will be tested at 69% and 88% of the OS events and at the OS final analysis. A

stratified log-rank test (1-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses with the overall significance level preserved at 0.025 (1-sided). OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding 95% CI.

9.3.2.2. Pathologic Complete Response

Pathologic complete response is defined as the absence of histologically identifiable residual cancer in any resected specimen. The pathogical complete response rate on each treatment arm will be estimated by dividing the number of patients with pathogical complete response recorded from randomization until PD per modified RECIST v1.1 or death due to any cause by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm.

9.3.2.3. Objective Response

Objective response (OR) is defined as a CR or PR per RECIST v1.1 (Appendix 4) recorded from randomization until disease progression per modified RECIST v1.1 (Appendix 3) or death due to any cause. A patient will be considered to have achieved an OR if the patient has a CR or PR which does not need to be confirmed at a subsequent assessment. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the ORR analysis.

The ORR on each treatment arm will be estimated by dividing the number of patients with OR (CR or PR) by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm. The CR rate and PR rate analyses will be performed similarly. In addition, the best overall response for each patient will be summarized by treatment arm.

9.3.2.4. Duration of Response

Duration of response (DR) is defined, for patients with an objective response, as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of PD per modified RECIST v1.1 or death due to any cause, whichever occurs first. Censoring rules for DR will follow those described above for PFS. DR will be summarized by treatment arm using Kaplan-Meier method and displayed graphically, where appropriate. The median DR and 95% CI for the median will be provided for each treatment arm.

9.3.2.5. Locoregional Failure

Locoregional failure (LRF) is defined as the time from the date of randomization to the date of the first documentation of locoregional recurrence or death due to any cause, whichever occurs first. LRF will be summarized by treatment arm using Kaplan-Meier method and displayed graphically, where appropriate. The median LRF and 95% CI for the median will be provided for each treatment arm.

9.3.2.6. Distant Metastatic Failure

Distant metastatic failure or distant metastasis (DM) is defined as the time from the date of randomization to the date of the first documentation of distant metastatic or death due to any cause, whichever occurs first. DM will be summarized by treatment arm using Kaplan-Meier method and displayed graphically, where appropriate. The median DM and 95% CI for the median will be provided for each treatment arm.

9.3.2.7. Neck Dissection

The rate of neck dissection on each treatment arm will be estimated by dividing the number of patients with neck dissection recorded from randomization until PD per modified RECIST v1.1 or death due to any cause by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm.

The rate of pathologically-positive neck dissection and rate of pathologically-negative neck dissection will be analyzed in the same way as the rate of neck dissection.

9.3.2.8. Patient-Reported Outcomes

The FAS will be used for the PRO analysis.

NCCN-FHNSI-22 and EQ-5D-5L, will be scored according to their respective validation papers and user's guides. For the EQ-5D-5L, utility scores will be calculated using the published weights (tariffs) for the United Kingdom (UK). Specific country weights may be applied for country specific analyses as needed.

Summary statistics (mean and standard deviation [SD], median, range) of absolute scores will be reported for the total and subscales of the FHNSI-22, and the utility and VAS scores of the EQ-5D-5L.. The mean change of absolute scores from baseline (and 95% CI) will also be reported. Line charts depicting the means and mean changes of items and subscales over time will be provided for each treatment arm.

Symptoms of disease will be assessed using the DRS-P subscale of the NCCN-FHNSI-22 with a focus on the single item 'I can swallow easily and naturally'. HRQoL will be assessed using the FWB subscale of the NCCN-FHNSI-22 and also the EQ-5D-5L.

Treatment arms will be compared using percent of patients with improvement in swallowing, defined as a 1-point increase on the 5-point Likert scale maintained for 2 consecutive assessments, in the single 'swallowing' item of the FHNSI-22. A chi-square test will be used for the analysis including patients in the FAS with a baseline score and at least one post-baseline assessment.

Treatments arms will be compared based on time to deterioration (TTD) of 1) HRQol, 2) disease-related symptoms-physical, and 3) 'swallowing'. TTD is defined as the time from randomization to deterioration where deterioration is defined, respectively, as 1) a 3 point decrease on the FWB scale for health-related quality of life (HRQoL), 2) a 3 point decrease on the DRS-P for symptoms of disease, and 3) a 1 point decrease on the 'swallowing' item of the FHNSI-22, in two consecutive assessments. The time to event will be calculated using

the date of the baseline assessment and the date of first of the two consecutive assessments use to identify the event. Note that a decline in FWB subscale of the FHNSI-22 represents a worsening in HRQol. A decline in DRS-P score represents an increase in physical symptoms of disease. A decline in the 'swallowing' item score represents a decrease in the ability to swallow naturally and easily.

Patients will be censored at the last time when they completed a PRO assessment if they have not deteriorated prior to death, lost to follow-up or the last scheduled PRO assessment.

TTD associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25^{th}, 50^{th}, and 75^{th} percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CIs.

Treatment arms will be compared based on mean scores of the FHNSI-22 total, subscales and the EQ-5D-5L utility and VAS scores obtained from repeated measures, mixed-effects regression models that contain the baseline score as a covariate. Other exploratory PRO analyses may be performed subsequently.

9.3.2.9. Analysis of Pharmacokinetics

The central laboratory, analytical laboratories (eg, PK, ADA, NAb), and Pfizer clinical assay group (CAG) colleagues will be unblinded. If the need arises for early analysis of the PK concentration analysis set (before database lock and release of the randomization codes for the study), a PK unblinding plan will be developed. A PK analyst, who is not associated with the study team, will conduct the analysis to avoid unblinding of the study team.

9.3.2.9.1. Pharmacokinetic Analysis of Avelumab

C_{max} and C_{trough} for avelumab will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean ratios, its associated CV, and 95% CI) by study phase, cycle (if applicable), and day. The trough concentrations for avelumab will be plotted using a box-whisker plot by study phase, cycle (if applicable), and day in order to assess the attainment of steady-state in Arm A.

Additionally, avelumab PK will be evaluated following cisplatin dosing by comparing the overall geometric mean ratios of C_{max} and C_{trough} in only Arm A on Day 8 of the CRT Phase to Day 1 of the Lead-in Phase.

9.3.2.9.2. Pharmacokinetic Analysis of Cisplatin

Standard plasma PK parameters for cisplatin (total and free) will be estimated using non-compartmental and/or compartment methods, if needed. Analyses will include C_{max}, time to T_{max}, AUC_{inf}, $t_{½}$, CL, and Vz as data permit.

Dose-normalized parameters (eg, CDN-C_{max}, DN-AUC_{inf}) will be reported as appropriate. Descriptive statistics for the PK parameters for cisplatin will be provided in tabular form. Cisplatin plasma concentrations will be summarized descriptively (n, mean, SD, CV, median,

minimum, maximum, geometric mean, its associated CV, and 95% CI) by nominal time. Individual patient and median profiles will be presented on both linear-linear and log-linear scales.

Additionally, cisplatin PK (total and free) will be evaluated following avelumab or placebo dosing by comparing the overall geometric mean ratios of C_{max} and AUC_{inf} on Day 1 of the CRT Phase in Arm A to Day 1 of the CRT Phase in Arm B.

9.3.2.10. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

PK and PD data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab exposure and biomarkers or significant efficacy and safety endpoints. The results of these analyses, if performed, may be reported separately.

In addition, the relationship between exposure and efficacy and safety endpoints may be explored, as necessary, based on emerging efficacy and safety data. The analysis details will be provided in the Population Modeling Analysis Plan. The results of these modeling analyses may be reported separately from the clinical study report. The analyses will include subjects in both the FAS and the safety analysis set.

9.3.2.11. Immunogenicity Analysis

All analyses will be performed on the immunogenicity analysis set.

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies each will be summarized by phase (Lead-in, CRT, or Maintenance) and overall. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection, and immune status of the patients, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

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9.5. Safety Analysis

The safety analysis set will be the primary population for safety evaluation. Summaries of AEs and other safety parameters will be provided, by treatment arm, as appropriate.

9.5.1. Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible (http://ctep.info.nih.gov/reporting/ctc.html). The frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term will be reported. Adverse events will be graded by worst NCI CTCAE v4.03 severity grade, and will be summarized by relatedness to study treatment.

Emphasis in the analysis will be placed on AEs classified as treatment emergent. Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade ≥3, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for AEs of clinical interest may be further assessed as described in the SAP.

Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study treatment, action taken, and clinical outcome. Acute toxicities and late toxicities will also be summarized separately.

9.5.2. Laboratory Abnormalities

Laboratory test results will be graded according to the NCI CTCAE v4.03 severity grade. The frequency of patients with laboratory test abnormalities will be summarized according to the worst grade for each laboratory test.

For laboratory tests without an NCI CTCAE grade definition, results will be categorized as normal (within normal ranges), abnormal, or not done.

Shift tables will be provided to examine the distribution of laboratory abnormalities.

9.5.3. Electrocardiograms

ECG measurements will be used for the statistical analysis and all data presentations. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points. QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, heart rate (HR), and RR, PR, QRS, QTc intervals.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post baseline corrected QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment. Patients

experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

9.6. Interim Analysis

The interim analysis will be performed based on the FAS. Any safety evaluation at the time of the interim analysis will be based on the safety analysis set.

The goals of the interim analysis for PFS are to allow early stopping of the study for futility or determination of superiority of Arm A compared to Arm B based on PFS.

The study is designed to have 1 interim analysis and the final analysis based on the primary PFS endpoint. A formal efficacy boundary (O'Brien-Fleming) for rejecting the null hypothesis is constructed by using the spending function methodology of Lan-DeMets. To protect the integrity of the study and to preserve the type 1 error rate, a fraction of α (0.0097) for efficacy will be spent at the interim analysis and accounted for in the overall type 1 error rate if the interim analysis is performed exactly at the planned number of PFS events. The nominal significance levels for the interim and final efficacy analyses of PFS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. The overall significance level for the efficacy analysis of PFS will be preserved at 0.025 (1-sided test). The futility boundary is non-binding and will be determined based on a Gamma Family (-7) β-spending function.

The interim analysis of PFS will be performed after all patients have been randomized in the study and approximately 217 PD events per modified RECIST v1.1 or deaths (75% information fraction) have occurred. If the value of the test statistic exceeds the efficacy boundary ($z < -2.338$, $p < 0.010$), then superiority of Arm A compared to Arm B could be declared. If the value of the test statistic exceeds the futility boundary ($z > -0.728$, $p > 0.233$), then the study may be stopped for futility. Since the observed number of events at the interim analysis may not be exactly equal to the planned 217 PFS events, the efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-and β-spending functions.

If the results of the interim analysis indicate serious safety concerns, the sponsor, in conjunction with an external Data Monitoring Committee (E-DMC), will communicate with the Health Authorities regarding stopping the clinical trial.

OS will be compared between the 2 treatment arms using a hierarchical testing procedure, provided the primary endpoint, PFS, is statistically significant favoring Arm A. A maximum of 5 analyses are planned for OS: at the time of the interim analysis for PFS, at the time of the final analysis for PFS, after 270 deaths are observed, after 345 deaths are observed, and a final analysis for OS after 392 deaths are observed. An α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the one used for the primary efficacy analysis will be used to preserve the 0.025 overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses. The trial allows for the stopping of the study for a superior OS result, provided the

primary endpoint, PFS, has already been shown to be statistically significant favoring Arm A.

9.7. Data Monitoring Committee

This study will use an E-DMC comprised of 2 independent clinicians and 1 independent statistician.

The E-DMC will be responsible for ongoing monitoring of the safety throughout the study, and the evaluation of efficacy at the interim analysis according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision.

Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The E-DMC will review unblinded safety data.

- The first review will occur after 30 patients have been randomized, treated, and followed for at least 12 weeks. No patient enrollment hold is planned. The E-DMC assessment will be conducted based on the available safety data of the first 30 patients treated and on all the available data of other patients treated up to the time of data cutoff.

- Subsequent safety review will occur every 6 months thereafter, or as recommended by the E-DMC.

In addition, the E-DMC will be informed of suspected unexpected serious adverse reactions (SUSARs) as soon as these are communicated to Health Authorities.

To ensure ongoing close monitoring of safety in the study, Pfizer clinical and safety teams perform routine monitoring of the incoming safety data and evaluate safety issues potentially impacting the product benefit-risk profile in a timely manner per the Safety Review Plan. The data reviewed includes weekly updates of AEs and laboratory assessments documented in the clinical database and SAE information reported in the Pfizer safety database. Safety signals identified from review of clinical study safety data are escalated at any time to the multidisciplinary product Risk Management Committee. In addition, if a requirement for further evaluation and assessment is identified, including possible need to review unblinded safety data, the clinical study team may escalate the issue to an internal Safety Review Committee.

During the initial enrollment period, prior to the first formal E-DMC review of the safety data after 30 patients have been randomized, treated, and followed for at least 12 weeks, close monitoring and frequent communication between investigators and Sponsor clinical and safety personnel will be undertaken. It is anticipated that such communication will be

approximately weekly and immediately upon any significant change in patient clinical status, AEs, laboratory abnormalities or other potential safety concerns.

Relevant safety information is conveyed in a timely manner to regulatory authorities and relevant parties in accordance with international principles and prevailing regulations as well as to the EDMC. The E-DMC chairperson, as well as Pfizer, has discretion to request ad-hoc meetings as judged necessary for safety evaluation.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source

documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records(eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents: eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In

that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the most current, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for GCP, and the Declaration of Helsinki.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient or his or her legally acceptable representative is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, when applicable, before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of avelumab alone or the combination of avelumab plus SOC CRT any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, patient to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

5HT3	5-Hydroxytryptamine3
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cell-Mediated
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC_{inf}	Area Under the Concentration – Time Curve Extrapolated to Infinity
$AUC\tau$	Area Under the Concentration – Time Curve to the End of the Dosing Period
BMI	Body Mass Index
BID	Twice Daily
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CAG	Clinical Assay Group
CFR	Code of Federal Regulations
CG	Cockcroft-Gault
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum Concentration
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report Form
CRP	c-Reactive Protein
CRT	Chemoradiotherapy
CSA	Clinical Study Agreement
CSF	Colony Stimulating Factor
CT	Computerized Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events (US NCI)
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
C_{trough}	Trough Concentration
CTV	Clinical Target Volume
CV	Coefficient of Variation
D5NS	Potassium Chloride in 5% Dextrose and Sodium
DDP	cis-diamminedichloridoplatinum
DR	Duration of Response
DLT	Dose-Limiting Toxicity

DM	Distant Metastatic Failure or Distant Metasis
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DRS	Disease-Related Symptoms
DRS-E	Disease-Related Symptoms – Emotional
DRS-P	Disease-Related Symptoms – Physical
DU	Dispensable Unit
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
E-DMC	External Data Monitoring Committee
CCI	[redacted]
EDP	Exposure During Pregnancy
EOT	End of Treatment
EQ-5D-5L	EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire
EU	European Union
EudrCT	European Clinical Trials Database
FAS	Fas Cell Surface Receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	Fludeosyglucose
FFPE	Formalin Fixed, Paraffin Embedded
FHNSI-11	FACT/NCCN Head/Neck Symptom Index-22
FSH	Follicle-Stimulating Hormone
FWB	Functional Well-Being
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
GVHD	Graft Versus Host Disease
H1	Histamine 1 Receptor
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCl	Hydrogen Chloride
HCV	Hepatitis C Virus
HDPE	High Density Polyethylene
HMGB1	High-Mobility-Group Box 1
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Committee Harmonization

ICON-S	International Collaboration on Oropharyngeal Cancer Network for Staging
ID	Identification
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMRT	Intensity-Modulated Radiation Therapy
IND	Investigational New Drug
INF	Interferon
INN	International Nonproprietary Name
INR	International Normalized Ratio
IP	Investigational Product
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
IUD	Intrauterine Device
IV	Intravenous
IWR	Interactive Web-Based Response
JCO	Journal of Clinical Oncology
kg	Kilogram
LA	Locally-Advanced
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLQ	Lower Limit of Quantitation
LRF	Locoregional Failure
mAb	Monoclonal Antibody
MACH-NC	Meta-analysis of Chemotherapy in Head and Neck Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
N	Nodal (Stage)
N/A	Not Appliable
nAb	Neutralizing Antibody
NaCl	Sodium Chloride
NaOH	Sodium Hydroxide
NASBA	nucleic-acid sequence-based amplification
NCCN	National Cancer Comprehensive Network
NCI	National Cancer Institute
NK-1	Neurokinin 1
NS	Normal Saline
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate

OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PD	Progressive Disease
PD-1	Programmed Death Protein-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death Ligand 2
PEG	Percutaneous Endoscopic Gastrostomy
PES	Polyether Sulfone
PET	Positron Emission Tomography
PFS	Progression-Free Survival
CCI [redacted]	[redacted]
PK	Pharmacokinetics
PI	Principal Investigator
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PT	Prothrombin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q4W	Every 4 Weeks
Q16W	Every 16 Weeks
Q24W	Every 24 Weeks
QA	Quality Assurance
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable Disease
SD	Standard Deviation
SIB	Simultaneous Integrated Boost
SOA	Schedule of Activities
SOC	Standard of Care
SRSD	Single Reference Safety Document
SST	Serum Separator Tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Tumor (Stage)
TCR	T-cell receptor
t½	Elimination half life
TEAE	Treatment-emergent Adverse Event

TLS	Tumor Lysis Syndrome
T_{max}	Time to maximum plasma concentration
TNM	Tumor, Node, Metastases (Staging)
TSE	Treatment Side Effects
TSH	Thyroid Stimulating Hormone
TTD	Time to Deterioration
TTR	Time to Tumor Response
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
V_d	Volume of Distribution
V_z	Volume of Distribution
v	Version
WBC	White Blood Cell
WHO	World Health Organization

Appendix 2. ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature; eg, light house work or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 3. Modifications to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Guidelines Specific to Study B9991016

Tumor-related endpoints in this study will be based on Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 (Appendix 4) modified with respect to the definition of what constitutes **progressive disease** (PD) as follows. Any of the following will constitute PD per modified RECIST v1.1:

- Locoregional disease progression per RECIST v1.1 which is subsequently confirmed by pathology. Pathologic confirmation of progression will verify that radiographic changes represent true tumor progression and not radiation effects or non-malignant contrast enhancement.
- Locoregional clinically detectable progression that is confirmed by pathology.
- Surgical removal (salvage) of primary tumor with tumor present on final pathology.
- Salvage neck dissection >20 weeks (140 days) after completion of CRT with tumor present on final pathology.
- Metastatic (distant metastases) disease progression per RECIST v1.1. Confirmation of pathology is recommended unless medically contraindicated or lesion location too high risk for biopsy.

Pathologic evaluation of resected or biopsied specimens must be completed by a trained and medically qualified expert (eg, specialty board certified pathologist).

Pathologic complete response is defined as the absence of histologically identifiable residual cancer in any resected specimen.

Local failure is defined as residual or recurrent viable tumor on pathologic evaluation from the site of original tumor location. Presence of tumor is required for declaration of a progression event which requires identification of viable tumor cells on final pathology. Tumor reappearing within the initial and immediately adjoining anatomical region of the primary will be considered local recurrence.

Regional failure is defined as residual or recurrent viable tumor on pathologic evaluation from the regional lymph node basins (eg, neck nodes). Presence of tumor is required for declaration of a progression event which requires identification of viable tumor cells on final pathology.

Distant metastatic disease is defined as new tumor identified at a site distant from the head and neck anatomic region or draining lymph nodes. Biopsy of any presumed distant metastatic disease is strongly recommended. A solitary, speculated lung mass/nodule is a second primary neoplasm and is not a disease progression event unless proven otherwise by biopsy in a patient with a smoking history. Multiple lung nodules/masses are considered

distant metastases from the index cancer and constitutes a disease progression event unless proven otherwise by biopsy.

Irradiation of the primary tumor and radiographically enlarged lymph nodes is considered part of the treatment under investigation in this clinical trial and therefore these target lesions remain evaluable lesions for response assessment.

It is expected that the status of the primary tumor is assessed thoroughly at the beginning of the surgical procedure before undertaking nodal dissection. Presence of persistent disease at the primary site, confirmed by frozen section will be considered disease progression.

Neck dissection parameters are described in Section 3.4 and will consist of a selective neck dissection unless a cytologic sampling of the nodes that appear enlarged is negative.

Positive neck specimens removed within 140 days after completion of CRT will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures.

Appendix 4. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-Measurable Disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion patiented to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

  - One or more target measurable lesions have not been assessed;

    or

  - Assessment methods used were inconsistent with those used at baseline;

    or

  - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    or

  - One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective/Patientive Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in Table.

Objective Response Status at each Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate or Missing	No	SD
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement. Confirmation of CR or PR is not required as this trial is randomized and double-blinded. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Appendix 5. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 4.03, dated 14 June 2010) has been placed in the Study Reference Binder for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

Appendix 6. NCCN FHNSI-22

Do not copy for patient administration.

NCCN-FACT FHNSI-22 (Version 2)

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

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HN3	I have trouble breathing	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	HN12	I have pain in my mouth, throat or neck	0	1	2	3	4
	GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
	HN7	I can swallow naturally and easily	0	1	2	3	4
	HN1	I am able to eat the foods that I like	0	1	2	3	4
	HN10	I am able to communicate with others	0	1	2	3	4
	HN11	I can eat solid foods	0	1	2	3	4
	GP5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP1	I have a lack of energy	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	Hep 5	I have had a change in the way food tastes	0	1	2	3	4
TSE	N6	I have mouth sores	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010
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Appendix 7. EuroQol EQ-5D-5L

Do not copy for patient administration.

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

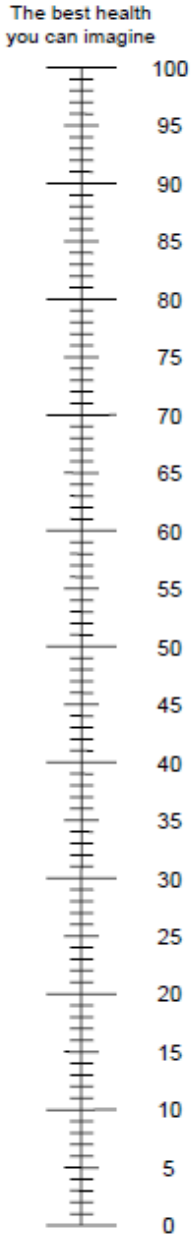
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]



Appendix 8. Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: ASCO Clinical Practice Guideline

Calculation Tools for Body Surface Area (BSA)

BSA Calculation Resources	
Formula Name	Formula
Chemotherapy is usually dosed by square meter of body surface area (BSA). BSA has been chosen rather than body weight as the basis for calculation for two reasons. First, BSA has been demonstrated to provide a more accurate comparison of activity and toxicity for certain drugs. Second, BSA can be more closely correlated with cardiac output, which determines the blood flow to the liver and kidneys, thus influencing drug elimination.	
Boyd	BSA (m^2) = 0.0003207 x Ht(cm) 0.3 x weight(g)(0.7285 – (0.0188 x LOG10weight(g)))
DuBois and DuBois	BSA(m^2) = Wt(kg)0.425x Ht(cm)0.725 x 0.007184
Gehan and George	BSA(m^2) = Wt(kg)0.51456x Ht(cm)0.42246x 0.0235
Haycock, et al.	BSA(m^2) = Wt(kg)0.5378x Ht(cm)0.3964x 0.024265
Mosteller (Adults and Children)	BSA(m^2) = SQR RT((Ht(cm) x Wt(kg))/3600) or BSA(m^2) = SQR RT((Ht(in) x Wt(lb))/3131)

Please note: Calculators using these formulas are available online

This practice tool for physicians is a dosing table derived from an ASCO® practice guideline. The practice guideline and this table are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This table does not recommend any particular product or course of medical treatment. Use of the practice guideline and this table is voluntary. The full practice guideline and additional information are available at http://www.asco.org/guidelines/wbd.

CCI

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Appendix 11. France Appendix

This appendix applies to study sites located in France.

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for investigational product.

3. Inspections

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.