TITLE:

REPORT; REirradiation and PD-1 blockade On Recurrent squamous cell head and neck Tumors

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1.0 TRIAL SUMMARY

Abbreviated Title	REPORT
Full title	REirradiation and PD-1 blockade On Recurrent squamous cell head and neck Tumors
Trial Phase	Phase I/II
Clinical Indication	Head and neck squamous cell carcinoma (HNSCC)
Trial Type	Exploratory
Type of control	NA
Route of administration	Intravenous
Trial Blinding	Open-label
Treatment Groups	Nivolumab, intravenous every 2nd week (1 cycle = 2 weeks), dose escalation schedule (1.0, 3.0 mg/kg), for a maximum of 12 months or until disease progression. In addition radiotherapy (RT) will be given to a total dose of 60 Gy (1,5 Gy fractions twice daily) for a total period of 4 weeks
Number of trial subjects	20
Estimated enrollment period	Q2 2017 – Q4 2018
Estimated duration of trial	The sponsor estimates that the trial will require approximately 2.5 years from the time the first subject signs the informed consent until the last subject's last on-treatment visit. Follow-up will continue 4 years after end of study therapy.
Duration of Participation	Each subject will participate in the trial until death, drop out, or loss-to follow-up from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, each eligible subject will receive nivolumab. Two weeks after start of nivolumab the patients will receive radiotherapy (RT) to a total dose of 60 Gy, given as 1.5 Gy fractions twice daily for a total period of 4 weeks. Treatment with nivolumab will continue until disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements, subject receives nivolumab for 12 months, pregnancy, or administrative reasons. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events [SAEs] will be collected for 90 days after the end of treatment). Patients without disease progression will have follow-up visits for 4 years after end of study therapy.

2.0 BACKGROUND AND RATIONALE

2.1 Rationale for study therapy

Radiotherapy (RT) is a main treatment modality across different cancer forms and is administered to approximately 50 % of all cancer patients. Radiation therapy is not curative in most cases, and the need for adjuvants is evident and unmet. There has emerged compelling evidence that radiotherapy is capable of inducing immunogenic cell death, which serves as a trigger for the immune system ("in situ vaccine"). Recently published preclinical and clinical data indicate that localized radiotherapy can evoke and/or modulate tumor-associated immune responses, resulting in systemic anti-tumor activity(1). There is generally a high expression of PDL-1 in HNSCC(2), and the expression is enhanced by RT. HNSCC is among the most radiation sensitive cancers, while also considered immunogenic, partly due to the high and increasing frequency of tumors infected with human papiloma virus (HPV)(2). Moreover, HNSCC with T-cell infiltration is more sensitive to radiotherapy.

In this study, the aim is to release the brake on the immune response by use of nivolumab, an inhibitory antibody against PD-1. Importantly, the immune response may not only boost local tumor control, but lead to eradication of metastatic disease and hence bring patients to a curative situation. Nivolumab has previously been shown to be effective in phase III trials in melanoma, lung cancer and renal cell carcinoma. Recently the results from a phase III study in HNSCC was reported(3). This was, an open-label, randomized study of nivolumab versus investigator's choice of therapy in previously treated patients with HNSCC. The patients had tumor progression on or within 6 months of platinum therapy in the primary, recurrent, or metastatic setting. The trial randomized 361 patients 2:1 to receive either nivolumab 3 mg/kg intravenously every two weeks or investigator's choice (cetuximab/methotrexate/docetaxel) until documented disease progression or unacceptable toxicity. The primary endpoint was OS. The study was stopped early due to positive interim results in favour of nivolumab. At the interim analysis, which was conducted after 218 events, patients assigned to nivolumab were found to have a 30 percent reduction in risk of death compared with those assigned therapy of investigator's choice. Median overall survival was 7.5 months for those assigned nivolumab versus 5.1 months for those assigned therapy of investigator's choice. At 12 months, 36 percent of the patients treated with nivolumab were alive compared with 17 percent of those assigned therapy of investigator's choice. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. The safety profile for nivolumab was favorable compared to the investigator´s choice therapy, and consistent with prior studies. Treatment-related adverse events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy group

Despite aggressive multimodal treatment with chemoradiotherapy, hypoxic-modulators and surgery to cure HNSCC patients, recurrent and second primary tumors in previous irradiated area (>46 Gy) are a common clinical challenge. Re-irradiation to doses of 60 Gy or more is a possible treatment option, offering long-term survival for selected patients. However, the re-irradiation is complicated with serious acute and late toxicity. Recurrent disease is also associated with a high risk of developing systemic disease. There is a need for new treatment approaches and combinations to improve tumor control and reduce toxicity.

Radiotherapy is a powerful inducer of inflammation, and the expression of PD1-L1 is known to be enhanced by inflammatory cytokines, including IFNg. Experimental evidence from mice

models have shown that radiotherapy induces increased PD-L1 expression in tumor tissue. Moreover, there is evidence suggesting that HNSCC with T-cell infiltration is more sensitive to radiotherapy. There is thus a strong rationale for combing PD-1 inhibitors with radiotherapy. However, this potential remains largely unexplored in humans. We consider that head-and-neck cancer is a particularly attractive entity for investigating this therapeutic combination, because of i) the high radiosensitivity of this cancer form ii) the clinical efficacy of PD-1 inhibitors as monotherapy in early clinical trials iii) the availability of tumor biopsies for translational/biomarker research.

2.2 Nivolumab

Nivolumab is a fully human monoclonal antibody that binds to PD-1 with nanomolar affinity and a high degree of specificity, thus precluding binding of PD-1 to its ligands PD-L1 and PD-L2. Nivolumab does not bind other related family members, such as BTLA, CTLA-4, ICOS, or CD28. Nivolumab has been approved by FDA and EMA for treatment of metastatic melanoma, renal cell carcinoma (RCC) and NSCLC, based on phase III trials showing improved survival. Clinical trials have also demonstrated clinical activity of nivolumab against HNSCC (see above) and other cancers. Please refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on nivolumab.

2.3 Rationale for Dose Selection

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level (see IB). The RT given in the present study gives considerable side effects, related to inflammation that may be enhanced by PD1 blockade. Nivolumab has shown efficacy and mild toxicity when given as monotherapy for HNSCC at a dose of 3.0 mg/kg Q2W, which is the target dose in the present trial(3). To assess the toxicity, the following dosing schedule has been chosen: Nivolumab, intravenous every 2nd week (1 cycle = 2 weeks), dose escalation schedule (1.0, 3.0 mg/kg), for a maximum of 12 months or until disease progression. RT will be given to a total dose of 60 Gy (1.5 Gy fractions twice daily) for a total period of 4 weeks. We expect that any increased toxicity will be observed within 2 weeks after end of RT and thus allow for a 3.0 mg/kg Q2W dose level therafter. If a drug-related toxicity is observed, the guidelines outlined below will apply.

2.4 Risk/benefit considerations

The benefit-risk relationship has been carefully considered in the planning of the trial. Based on the preclinical and clinical data (see IB, (3) and above), the conduct of this trial is considered justifiable. Even though subjects in phase I/II clinical trials generally cannot expect to receive direct benefit, we believe the rationale for conducting this trial is sound, and it is a realistic chance that some patients could benefit from nivolumab in combination with radiotherapy. The routine treatment (i.e. radiotherapy or palliative chemotherapy alone) is not of major benefit for many patients in this group. The dose escalation schedule included in our trial design, and the moderate maxium dose of 3.0 mg/kg, mean that the risk of SAE related to nivolumab is limited. We thus consider that the risk-benefit ratio is favourable. Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

3.0 SAFETY MONITORING COMMITTEE

A safety monitoring committee (SMC) will monitor safety on a periodic basis. Members of the

SMC will be experienced clinicians. The SMC will meet approximately every 6 months from the point of first patient in (FPI) to review safety and study conduct data. The safety data will include demographic data, adverse events and relevant laboratory data. In addition the SMC will meet after finalization of each dose cohort (i.e. three patients has completed minimum 8 weeks of treatment), and in case DLT is experienced. See section 8.8 for definitions.

Following each data review, the SMC will provide recommendations to the Study Leadership as to whether the study should continue or be amended, or whether the study should be stopped on the basis of safety (i.e., evidence of harm). The Study Leadership will make a decision on the basis of the SMC recommendations.

Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

No interim efficacy analysis is planned.

4.0 OBJECTIVES & HYPOTHESES

4.1 Objectives

Primary objectives:

1) To determine the safety and tolerability of nivolumab when administered concomitant with high dose (60 Gy) re-irradiation in patients with locally advanced recurrent or second primary HNSCC
2) To determine a safe dose of nivolumab when administered concomitant with high dose (60 Gy) re-irradiation in patients with locally advanced recurrent or second primary HNSCC

Secondary objectives:

1) To evaluate progression-free survival after 12 months
2) To evaluate objective response rate (ORR) and duration of response (DOR), by RECIST v1.1 as primary method and immune-related RECIST (irRECIST) as secondary method
3) To evaluate overall survival

Exploratory objectives:

4) To investigate the immunological response, tumor evolution and dynamics in the tumor micrenvironment induced by the study therapy
5) To investigate biomarkers for development of clinical response, toxicity and immune response

4.2 Hypotheses

- Anti-PD1 mAb can safely be administered concomitant with re-radiation in HNSCC.

- The combination therapy can induce clinical response, immune response and dynamics in the tumor microenvironment.
- Genetical and immunological profiling of pre-treatment samples may identify biomarkers for predicting which patients will benefit from the therapy

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Subject Inclusion Criteria

- Age >18 years
- Recurrent or secondary primary squamous cell carcinoma originating from the oral cavity, oro/hypo-pharynx or larynx
- Prior radiotherapy (46-70Gy)
- Adequate newly obtained core or excisional biopsy of a recurrent tumor lesion
- Measurable disease
- Lesion available for biopsy during study treatment
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy > 12 months
- A minimum of 6 months since prior radiotherapy in the same area or minimum 4 weeks (28 days) since previous other cancer treatment
- Both HPV positive and HPV negative disease allowed
- Distant metastases allowed
- Adequate organ function based on clinical examination and lab values
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug
- Women must not be breastfeeding
- WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo five half-lives. The terminal half-life of nivolumab is up to 25 days

5.1.2 Subject Exclusion Criteria

- History of other prior malignancy, with the exception of curatively treated basal cell or squamous cell carcinoma of the skin, cervical cancer stage IB and stage I prostate cancer considered not necessary to treat
- Disease suitable for curative salvage surgery
- Treatment with any investigational medicinal product (IMP) that may interfere with the study treatment, within 4 weeks prior to first administration of study drug.

- Significant cardiac, pulmonary or other medical illness that would limit activity or survival
- Pregnancy or lactation.
- Known hypersensitivity to any of the components of the investigational product
- Patients who test positive for hepatitis B, C or HIV.
- Diagnosis of immunodeficiency or medical condition requiring systemic steroids or other forms of immunosuppressive therapy
- Autoimmune disease that has required systemic therapy within the past 2 years
- Any reason why, in the opinion of the investigator, the patient should not participate

5.2 Study treatment

The study will include 20 patients. The following treatment will be used:

- Radiotherapy (RT) to a total dose of 60 Gy, given as 1.5 Gy fractions twice daily for a total period of 4 weeks, will be delivered to the target volumes determined by PET-CT scan. Definition of target volumes and organs at risk will follow the Dahanca guidelines 2013 (published on www.dahanca.dk). The dose deliverd to organs at risk, determined by PET-CT scan, will also be calculated.

- Nivolumab administered intravenous every two weeks, starting two weeks (Cycle 1, Day 1) before start of radiotherapy. Nivolumab will be given for a maximum of 12 months or until disease progression.

- Nivolumab will be administered according to a dose escalation schedule (1.0 and 3.0 mg/kg), as shown in Figure 1. Three patients will be included at each dose level. During the dose escalation part the subsequent patient will start therapy with nivolumab 6 weeks after the previous to allow time to observe the possibility for acute toxicity. If no dose limiting toxicity (DLT) is observed at the first dose level, additional three patients will be included at the next dose level. If DLT is experienced see section 8.8 for details. The remaining patients will we treated at the maximum tolerated dose.

- The nivolumab dose will be adjusted to 3.0 mg/kg (standard dose used in NCT02105636) for all patients from Cycle 5, Day 1 (2 weeks after end of radiotherapy), irrespective of starting dose.

The study treatment is outlined in Table 1. Trial treatment should begin within 28 days of first interventional screening assessments. Details on preparation and administration of nivolumab are provided in the IB.

5.2.1 Study drug

The product storage manager at the local pharmacy should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.
Investigational product documentation must be maintained. That includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage,

administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).
Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

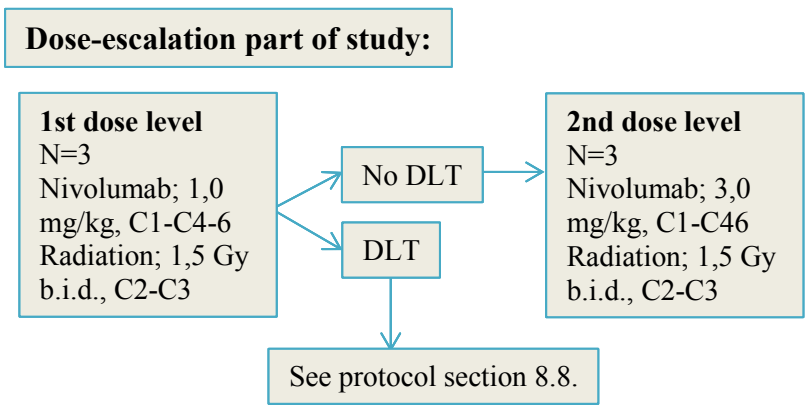
The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.
Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab.

The infusion will be administrated by nurses with experience in treatment with immunotherapy.

Table 1 Study Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Nivolumab	1,0 mg/kg	Q2W	IV infusion	Day 1 of each 2 week cycle	Experimental, Dose level 1
Nivolumab	3,0 mg/kg	Q2W	IV infusion	Day 1 of each 2 week cycle	Experimental, Dose level 2
Radiotherapy	1,5 Gy	BID		5 days a week, 4 weeks (Cycle 2 and 3)	Standard

Figure 1



5.3 Dose schedule and modification

5.3.1 Nivolumab Schedule

Continuation of nivolumab treatment with suspected progression is permitted, see Section 5.3.2.4. Treatment will continue for a maxiumum of 12 months, or discontinuation from study treatment due to any of the criteria listed in section 5.5.

If required, subjects may receive nivolumab up to 3 days before or after the scheduled date. A dose given more than 3 days after the intended dose date will be considered a delay. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

Subjects should be monitored for infusion reactions during nivolumab administration. If an acute reaction is noted, subjects should be managed according to Section 5.3.2.6. Doses of nivolumab may be interrupted, delayed or discontinued as needed.

5.3.2 Dose Modifications for Nivolumab

Dose modification is only allowed in case of Dose Limited Toxiticity (DLT). See section 8.8 for instructions. For dose delay, see 5.3.2.1

5.3.2.1 Dose Delay Criteria for Nivolumab

Dose delay criteria apply for all drug-related AEs. A treatment delay up to 4 weeks, i.e. 6 weeks calculated from the last dose, is allowed. A treatment delay beyond this must be discussed with the Study leadership. A treatment delay beyond 10 weeks is not allowed.

Tumor assessments should continue per protocol schedule, even if dosing is delayed.

Nivolumab administration should be delayed for the following reasons:

- Any Grade ≥ 2 non-skin drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade 3 skin drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality
- Any adverse event, laboratory abnormality, intercurrent illness or other reason which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated. Nivolumab dosing can be resumed on the established dosing schedule when retreatment criteria are met (Section 5.3.2.2).

5.3.2.2 Criteria to Resume Dosing for Nivolumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of grade 2 fatigue
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.

5.3.2.3 Treatment Discontinuation Criteria for Nivolumab

Nivolumab treatment should be permanently discontinued for the following:

- Any grade 4 drug-related toxicity
- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 5 x ULN for 2 weeks
    - AST or ALT >5 x ULN
    - Total bilirubin > 3 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that is not associated with symptoms or clinical manifestations of pancreatitis. The Study leadership should be consulted for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Study leadership.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
    - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed, if approved by the Study leadership.

- Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the Study leadership must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

For deailed information see the IB for nivolumab.

5.3.2.4 Continuing Nivolumab with Suspected Progression

Accumulating evidence indicates that a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression, eg, due to inflammatory reaction simulating progression ("tumor flare" or pseudoprogression). Subjects may, at investigator discretion and agreement with the Study leadership, continue nivolumab in the setting of suspected progression until progression is confirmed. If the investigator believes that the subject continues to derive clinical benefit by continuing treatment, the subject should continue monitoring/assessments according the same schedule as patinets without tumor progression, with more frequent radiologic assessment if clinically indicated (see below).

Subjects may continue nivolumab beyond initial (suspected) progression only if they meet the following criteria:

- Subject is in stable performance status (ECOG 0-1) and tolerating nivolumab
- Treatment will not delay intervention to prevent imminent complications
- Investigator-assessed overall clinical benefit

Radiographic assessment should be repeated after suspected progression as clinically required in order to determine whether there has been a decrease in the tumor size or continued progression. Potential for clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive benefit from continued treatment with nivolumab. Nivolumab treatment should be discontinued permanently upon confirmation of progression.

5.3.2.5 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immune oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure.

5.3.2.6 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For **Grade 2** symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with

methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

5.4 Concomitant Treatments

It is expected that enrolled subjects will have systemic corticosteroids tapered as quickly as clinically appropriate during screening phase, and discontinued if possible prior to inclusion.

Supportive care for all disease-related or treatment-related adverse events should be maximized for all subjects on this study.

5.4.1 Prohibited and/or Restricted Treatments

Immunosuppressive agents, including systemic corticosteroids, are prohibited during study treatment unless utilized to treat a drug-related adverse event. Subjects with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone or > 3 mg dexamethasone per day (or equivalent) or other immunosuppressive medications (including within 14 days of inclusion) are excluded. Subjects continuing to require supra-physiologic steroids (prednisone > 20 mg daily or > 3 mg dexamethasone per day or equivalent) may not be included. Inhaled or topical steroids, and adrenal replacement steroid doses ≤ 20 mg daily prednisone or ≤ 3 mg dexamethasone per day or equivalent, are permitted in the absence of active autoimmune disease.

5.4.2 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Steroid use should be minimized prior to inclusion. Systemic corticosteroid use or physiologic replacement doses of steroids are permitted, even if > 20 mg/day prednisone equivalents, for: a) treatment-related AEs or b) treatment of non-autoimmune conditions (eg, prophylaxis for contrast dye allergy, contact hypersensitivity). Details regarding corticosteroid use prior to and during the study will be collected (name of medication, doses utilized, start and stop dates, frequency of use, route of administration). Information regarding concomitant corticosteroid use may be analyzed with regard to study outcome measures. Subjects requiring chronic treatment with corticosteroids should be treated with histamine-2-receptor antagonists or proton pump inhibitors as prophylaxis for potential gastrointestinal adverse reactions (ulceration, perforation, hemorrhage) unless otherwise contraindicated.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs.

5.5 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.3 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- AE as described above (section 5.3.2.3).
- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 5.3.2.4
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up

- Administrative reasons

The End of Treatment visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, starting a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression, information on survival will be obtained until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of BMS decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 OUTCOME MEASURES

6.1 Primary Outcome Measures

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0.
- Changes in vital signs, physical findings, and clinical laboratory results

6.2 Secondary Outcome Measures

- PFS, defined as the time from inclusion to the time of radiographic progression (as assessed by RECIST) or death from any cause during the study
- Overall survival (OS), defined as the time from the date of inclusion to the date of death from any cause
- Objective tumor response rate (ORR), defined as the proportion of patients with an objective tumor response (either partial response [PR] or complete response [CR] per investigator using RECIST)
- Durable response rate (DRR), defined as the proportion of patients with an objective tumor response lasting at least 6 months
- Duration of objective response (DOR) among patients with an objective response
- PFS, ORR, DRR and DOR assessed by irRECIST v1.1

7.0 TRIAL FLOWCHART

Trial Period:	**Screening Phase**		**Treatment phase**[a]						**Post-Treatment**			
Treatment Cycle (C)/Title: (Each cycle is 2 weeks)	Informed consent (Visit 1)	Main Study Screening (Visit 2)	C1 D1	C2 D1	C3 D1	To be repeated until total treatment time of 12 months: C4 D1	To be repeated until total treatment time of 12 months: C5 D1	Treatment discontinuation	Safety Follow-up	Follow-up Year 1 after disc.	Follow-up Year 2-4 after disc.	Survival Follow-up
Scheduling Window (Days):		-14 to -1	± 3	± 3	± 3	± 3	± 3	At time of disc.	30 days post disc.	Every 3 months post disc.	Every 6 months	
Administrative Procedures												
Informed Consent[b]	x											
Inclusion/Exclusion Criteria		x										
Demographics and Medical History		x										
Prior and Concomitant Medication Review[c]		x										
Post-study anticancer therapy status										x	x	
Clinical Procedures/Assessments												
Review Adverse Events[d,e]		x	x	x	x	x	x	X	x	x		
Full Physical Examination		x				x			x			
Directed Physical Examination			x	x	x		x	X		x	x	
Vital Signs and Weight[f]		x	x	x	x	x	x	X	x	x	x	
ECOG Performance Status		x	x	x	x	x	x	X	x	x	x	
Electrocardiogram (ECG) [f]		x					x[f]					
Survival Follow-up												x
Laboratory Procedures/Assessments: analysis performed by local laboratory												
Pregnancy Test[g]		x					x					
PT/INR and aPTT[h]		x										
CBC with Differential[i]		x	x	x	x	x	x	X	x	x	x	
Comprehensive Serum Chemistry Panel[i]		x	x	x	x	x	x	X	x	x	x	
HIV, HBV and HCV test		x										
Urine analysis[i]		x				x		X	x	x[l]	x	
FT4 and TSH, anti TPO[ip]		x			x		x	X	x	x	x	
Treatment administration												
Nivolumab			x	x	x	x	x					
Radiation therapy				x	x							
Efficacy Measurements												
18F-FDG PET/CT[j]		x					x[k]	x[m]				
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival and Newly Obtained Tissue Collection[n]		x		x[r]	x[r]			x[r]				
Plasma and Serum Collection[o]		x		x	x	x	x	X		x[l]	x	

Trial Period:	**Screening Phase**		**Treatment phase**[a]						**Post-Treatment**			
Treatment Cycle (C)/Title: (Each cycle is 2 weeks)	Informed consent (Visit 1)	Main Study Screening (Visit 2)	C1 D1	C2 D1	C3 D1	To be repeated until total treatment time of 12 months: C4 D1	To be repeated until total treatment time of 12 months: C5 D1	Treatment discontinuation	Safety Follow-up	Follow-up Year 1 after disc.	Follow-up Year 2-4 after disc.	Survival Follow-up
Scheduling Window (Days):		-14 to -1	± 3	± 3	± 3	± 3	± 3	At time of disc.	30 days post disc.	Every 3 months post disc.	Every 6 months	
PBMC collection[o]		x		x	x		x	X		x[l]		

a. General, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines.

b. Written consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame in the protocol. Subject number will be assigned when the study informed consent is signed.

c. Prior medications – Record all medications taken within 30 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs.

d. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

e. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events that are believed to be related to prior treatment with study drug. For subjects included and never treated with study drug, SAEs should be collected for 30 days from the date of inclusion. All SAEs must be followed to resolution or stabilization.

f. Vital signs to include temperature, pulse, oxygen saturation, weight and blood pressure. Height will be measured at screening only. ECG is to be performed at screening , C5 day 1 and every 8th week thereafter, until disease progression or end of treatment with nivolumab.

g. For women of childbearing potential , a serum pregnancy test should be performed within 24 hours prior to first dose of trial treatment. Pregnancy tests (serum and/or urine tests) should be repeated every 5 cycles (10 weeks) ± 7 days.

h. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

i. Unresolved abnormal lab values that are drug related AEs should be followed until resolution. Lab tests do not need to be repeated after the end of treatment if lab tests are within normal range.

j. Tumor assessments by 18F-FDG PET/CT will be performed at screening, (Cycle 7), (Cycle 16) and at Month 12 (± 1 week). Tumor response will be evaluated using both and RECIST v1.1 (Appendix 15.3) and immune-modified RECIST criteria (Appendix 15.4). In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first.

k. Cycle 7 and Cycle 16, Month 12 and yearly thereafter until 5 years after start of treatment

l. For patients not progressed during treatment, urine analysis, plasma and serum, and PBMC collection to be performed at first FU visit only (12 weeks after discontinuation).

m. In subjects who discontinue study therapy, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 weeks). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory.

n. Fresh frozen and FFPE tumor biopsies before start of treatment (Cycle 1), before start of radiotherapy (Cycle 2), at Cycle 3 and at disease relapse/progression.

o. PBMC; at screening (or day 1 Cycle 1), and at Day 1 at the following cycles; Cycle 2, Cycle 3, Cycle 5, Cycle 9, Cycle 16 and at disease progression. 100 ml ACD blood at baseline. 50 ml ACD blood at later time points. To be taken before infusion of IMP. Plasma and serum will be collected at screening (or day 1 Cycle 1), Cycle 2 (Day 1 and 8), Cycle 3 (Day 1 and 8), Cycle 4 (Day 1), Cycle 5 (Day 1), Cycle 9 (Day 1), Cycle 16 (Day 1), Month 12 and at disease progression.

p. Thyroid function testing is to be done every 6 weeks during nivolumab treatment.

r. The sample collection is optional

8.0 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the Investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

8.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the trial.

8.1.1.3 Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

8.1.1.4 Prior and Concomitant Medications Review

8.1.1.4.1 Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.1.4.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the subject during the trial.

8.1.1.5 Disease Details and Treatments

8.1.1.5.1 Disease Details

The Investigator or qualified designee will obtain prior and current details regarding disease status.

8.1.1.5.2 Prior Treatment Details

The Investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

8.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The Investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

8.1.1.6 Assignment of Subject Number

All consented subjects will be given a unique subject number that will be used to identify the subject for all procedures that occur during the screening period, and for all subjects eligible for treatment, during the treatment and follow-up period.
Each subject will be assigned only one subject number. Subject numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original subject number assigned at the initial screening visit.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Status, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose of study drug. Concomitant medications including steroid dose will be collected within 14 days prior to first dose of study drug through the study treatment period.

Baseline local laboratory assessments should be done within 14 days prior to first dose and are to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase,lipase, TSH, free T4, and urine analysis.

The following baseline local laboratory assessments should be done within 28 days prior to first treatment: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA).

Pregnancy testing must be performed within 72 hours prior to Day 1 and then every 5 cycles (10 weeks) ± 7 days.

While on-study the following local laboratory assessments are to be done within 3 days prior to each dose: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin (if clinically indicated), Ca, Mg, Na, K, Cl, phosphate, LDH, glucose, amylase, and lipase. Thyroid function testing is to be done every 6 weeks.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in person or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

The start and stop time of the study therapy infusions should be documented.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

8.1.2.1.1 Full Physical Exam

The Investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening and at Day 1, at Cycle 4 and Cycle 8, and Day 1 at every fourth cycle onwards during study treatment as well as at the 30 days safety follow-up visit.

8.1.2.1.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

8.1.2.1.3 Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, oxygen saturation, weight and blood pressure. Height will be measured at screening only.

8.1.2.1.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment, at discontinuation of trial treatment and during follow-up as specified in the Trial Flow Chart.

8.1.2.2 Tumor Imaging and Assessment of Disease

The imaging assessments will be performed by 18F-FDG PET/CT. The tumor response will be assessed according to RECIST v1.1 as primary method and and by Immune Modified Response Evaluation Criteria in Solid Tumors (imRECIST) as secondary method. After baseline tumor assessments, evaluation of tumor response will be performed at Cycle 7, Day 1 (± 7 days), Cycle 16, Day 1 (± 7 days), at 12 months (± 10 days) from the date of first dose, and every 12 months thereafter (± 21 days) until 5 years after the first dose. Additional 18F-FDG PET/CT scans or other radiological evaluations will be performed if indicated.

8.1.2.3 Tumor Tissue Collection and Correlative Studies Blood Sampling

Fresh frozen and FFPE tumor biopsies will be obtained before start of treatment with nivolumab (Cycle 1), and thereafter optional before start of Cycle 2 (start of radiotherapy), at start of Cycle 3, and at disease relapse/progression.

PBMCs will be collected before start of treatment with nivolumab, and at Day 1 at the following cycles; Cycle 2, Cycle 3, Cycle 5, Cycle 9, Cycle 16 and at disease progression. Plasma and serum will be collected at baseline, Cycle 2 (Day 1 and 8), Cycle 3 (Day 1 and 8), Cycle 4 (Day 1), Cycle 5 (Day 1), Cycle 9 (Day 1), Cycle 16 (Day 1), Month 12 and at disease progression. For patients not progressing on study treatment, PBMCs and plasma and serum will also be collected 12 weeks after end of nivolumab therapy.

8.1.2.4 Laboratory tests

Laboratory tests for hematology, chemistry, urin analysis and other relevant tests are specified in Table 2. The lab results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Table 2 Laboratory Tests

Hematology	**Chemistry**	**Urine analysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	
Platelet count	Alanine aminotransferase (ALT)	Protein	INR
WBC (total and differential)	Aspartate aminotransferase (AST)		aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam if abnormal results are noted	
Absolute Neutrophil Count	Total protein		Free tyroxine (T4)
Absolute Lymphocyte Count	CRP	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Creatinine		TPO
	Uric Acid		
	Calcium		
	Chloride		Amylase
	Glucose		Lipase
	Phosphorus		HBV sAg and HCV Ab or HCV RNA
	Potassium		HIV-test
	Sodium		
	Magnesium		PBMC
	Total Bilirubin		Plasma, serum
	Direct Bilirubin *(If total bilirubin is elevated)*		
† Perform on women of childbearing potential only.			

8.1.2.5 Thyroid Function Testing

At Screening, thyroid function testing is to include TSH and free T4. At subsequent time points, thyroid function testing consists of TSH only. However, if the TSH is abnormal testing of free T4 is to be performed.

Management algorithms for suspected endocrinopathy adverse events (including abnormal thyroid function) can be found in the nivolumab investigator brochure.

8.1.3 Other Procedures

8.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.

8.1.3.2 Screening Period

Approximately 28 days prior to subject allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 14 days prior to the first dose of trial treatment.

- For women of childbearing potential, a serum pregnancy test will be performed within72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

- The baseline tumor biopsy has to be obtained within 28 days prior to the first dose.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

8.1.3.3 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

8.1.3.4 Post-Treatment Visits

8.1.3.4.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or stabilization, until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

8.1.3.4.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase. The remaining patients will move into the FollowUp Phase after end of nivolumab treatment. The patients should be assessed every 3 months the first year after discontinuation (± 7 days), the following three years (year 2-4 after discontinuation of study treatment) every six month, to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death and end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

8.1.3.4.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase. We will then monitor survival status by contacting the GP/local hospital or by phoning the patient every 3 month, until the end of the study. The survival status and, if applicable, the cause of death, will be recorded.

8.2 End of study

The end of study is defined as 5 years after inclusion of the last patient.

9.0 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

9.1 Management of adverse events

For recommendations on the management of adverse events, please see the last updated version of the Investigator´s Brochure for nivolumab.

9.2 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 8.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 8 for reporting details).

NOTE:
The following hospitalizations are not considered SAEs in this study:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- admission for administration of anticancer therapy in the absence of any other SAEs

9.2.1 Serious Adverse Event Collection and Reporting

The Investigator Brochure (IB) represents the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 90 days of the last dose of nivolumab. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). For subjects included and never treated with study drug, SAEs should be collected for 30 days from the date of inclusion.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

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

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies, must be reported to Sponsor (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).

If only limited information is initially available, follow-up reports are required.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

9.3 Nonserious Adverse Events

9.3.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug until 90 days from the last dose of study drug.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

9.4 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.5 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the Sponsor of this event and complete and forward a Pregnancy Form to Sponsor within 24 hours of awareness of the event and in accordance with SAE reporting procedures.

In this case, the study drug will be permanently discontinued in an appropriate manner.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor. Information on this pregnancy will be collected on the Pregnancy Form.

9.6 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

9.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.8 Dose Limitied Toxicity (DLT)

We foresee that DLT related to Grade 3 and/or 4 dermatitis and mucositt may be experienced.

During dose escalation phase: If a patient experience a possibly nivolumab-related Grade 3 adverse event at any dose level, an additional patient will be included at this dose level. If one more patient experience the same Grade 3 event on the same dose level (i.e. 2 of 4 patients at one dose level experiences the same Grade 3 event), this will be defined as DLT reached, and the dose should be reduced by one level. If DLT is experienced at the lowest dose level (1,0 mg/kg), the dose will be reduced to 0.3 mg/kg. If two patients experience DLT at this dose level, the study will be terminated. If a patient experiences a Grade 4 event, the dose should immediately be reduced by one level.

The Safety Monitoring Committee (SMC) will meet in the case of DLT, to discuss futher progress related to doses of nivolumab, and whether the protocol should be amended. In

addition, the SMC will meet after every time three patients have completed each dose level (i.e. completed the re-radiation), to discuss whether it will be safe to move to next dose level. No further patients will be included until the SMC has met. After the dose escalation phase has been completed, the SMC will meet if two patients experience AE grade 3 or one patient experiences AE Grade 4, considered related to nivolumab. No further patients will be included until the SMC has met.

The SMC is a group of oncologists located at the Clinical Cancer Research Unit, with experience in immunotherapy treatment. The members will not be involved in the study design or the study treatment.

9.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.9.1 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

9.10 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to Competent Authorities and Investigators in accordance with applicable national laws and regulations.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the Competent Authority according to national regulation. The following timelines should be followed:

The sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority concerned in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other SUSARs will be reported to the Competent Authority concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARs will be reported using the CIOMS form since Oslo University Hospital (sponsor) is not connected to EudraVigilance.

10.0 COLLATERAL RESEARCH.

An extensive research program will be conducted. The patient informed consent form will allow for performing biomarker analyses, immunological studies, gene profiling and studies of tumor evolution/heterogeneity during treatment, as well as comparison with data/material from other studies.

10.1 Biobanking:

Please see the study flow chart for information on the time points for collection of biopsies and peripheral blood.

- Tumor biopsies collected pre, during and post therapy (time of progression). If sufficient tissue is avaliable, the tumor will be cut into two/three pieces:
    - Fresh tumor cells/ tumor infiltrating lymphocytes frozen as cell suspension for CYTOF/flow cytometry, analysis of T cell specificity with multimers and functional immune assays
    - Snap-frozen tumor biopsies
    - FFPE tissue

- Peripheral blood samples collected pre-, during and post-therapy:
    - Peripheral blood mononuclear cells, processed with gradient centrifugation and frozen on liquid nitrogen
    - Plasma/serum, separated and frozen.

10.2 Plans for translational research addressing exploratory endpoints

The list below does not represent a mandatory list of assays that are to be performed, but provides an overview of the current plans. The prioritation of assays will be subject to review during the trial. Additional assays may be performed, reflecting ongoing developments in the field. Some of these assays will only be performed on selected patients, due to cost and work load.

1. Gene profiling with selected panels
2. Pathology/immunohistochemistry on all patients (incl. PD-L1, markers for immunogenic cell death and for lymphocyte and macrophage subpopulations)
3. DNA exome seq. of tumor and normal PBMCs on selected patients (mutations, HLA types/loss, SNPs in immune pathways)
4. RNA transcriptome sequencing of tumor on selected patients (gene expression profiles, neoantigens)
5. Serum biomarkers/soluble biopsies, including
    a. circulating DNA
    b. circulating micro RNA
    c. Bioplex cytokine- and MMP panels
6. Characterization of cell suspensions from tumor and peripheral blood:

a. CYTOF (investigating subpopulations/heterogeneity/evolution, both within tumor cells, immune cells and other stromal cells; relate CYTOF data to gene profiling and mRNA expression)
b. Flow cytometry, including the use of panels for regulatory T cells and myeloid suppressor cells(4)

7. Test of T cell reactivity against HPV-antigens, common tumor antigens and the individual spectrum of antigens in each patient´s tumor, identified through tumor sequencing/epitope prediction.
    a. Functional T cell assays, incl. ELISPOT, proliferation, Bioplex cytokine profiling, multimers (5, 6)
8. Tumor gene profiling for investigating tumor evolution/hetergenousity during treatment. Possible validation with mass spectrometry, CyTOF and IHC.

11.0 STATISTICAL ANALYSIS PLAN

11.1 Statistical Analysis Plan Summary

In this exploratory phase I study no formal hypothesis testing will be performed. Hence, the primary endpoint and secondary endpoints will be evaluated only by descriptive methods. Data will be described with proportions (percentage) for categorical data and with median, mean and range for continuous data. Kaplan-Meier curves will be produced for PFS and OS.

Progression free survival (PFS), defined as the time from inclusion to the occurrence of disease progression, as determined by investigators from tumor assessments per RECIST, or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date.

Overall survival (OS) will be calculated from the date of first dose of nivolumab until death. Patients alive at the time of data analysis will be treated as censored.

Exploratory analyses will be carried out to evaluate the data of the immunological and molecular analyses (e.g. biomarker studies) carried out. The statistical analyses will be dependent on the biological factors investigated and the analysis methodology used, and will be defined separately for each molecular study. With regard to some of the secondary/exploratory objectives, comparative analyses between groups or between samples obtained at different time points will be performed.

A number of 20 patients is considered suitable for addressing the primary endpoints, i.e. evaluating the safety and dose in the selected patient population. The biobank material obtained at consecutive time points from 20 patients should be sufficient for informative collateral studies.

12.0 EHICAL CONSIDERATIONS

12.1 Compliance with Laws and Regulations

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), in addition with the E.U. Clinical Trial Directive (2001/20/EC).

12.2 Informed Consent

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

12.3 Ethics Committee

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information will be submitted to the Ethics Committee, reviewed and

approved according national regulations before the study is initiated. This is also valid for any amendments and/or a new version of the study protocol (Amended Protocol).

12.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the Competent Authority, Sponsor and monitors.

13.0 ADMINISTRATIVE AND REGULATORY DETAILS

13.1 Study Documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of EC and governmental approval.

13.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

13.3 Monitoring

The investigator/site will be visited on a regular basis by the Clinical Study Monitor, who will assess compliance with the trial protocol and general principles of Good Clinical Practice. The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

13.4 Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

13.5 Data Management

The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. Detailed information regarding Data Management procedures for this protocol will be provided separately.

13.6 Publication Policy

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

14.0 LIST OF REFERENCES

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6. Bentzen AK, Marquard AM, Lyngaa R, Saini SK, Ramskov S, Donia M, et al. Large-scale detection of antigen-specific T cells using peptide-MHC-I multimers labeled with DNA barcodes. Nat Biotechnol. 2016.

15.0 ABBREVIATIONS

Abbreviation/Term Definition	Definition
ACD	Acid Citrate Dextrose
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BSA	Body Surface Area
BTLA	B And T Lymphocyte Associated
BUN	Blood Urea Nitorgen
CRF	Case Report Form (electronic/paper)
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
CYTOF	CYtometry Time Of Flight
DILI	Drug Induced Liver Injury
DLT	Dose Limited Toxicity
DOR	Duration Of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ERC	European Research Council
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraphin Embedded
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
HR	Heart Rate
IB	Investgators Brochure
ICH	International Conference on Harmonization
ICOS	Inducible Costimulator Protein
IFN	Interferon
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
mAb	monoclonal Anti body
MDSC	Myeloid-derived Suppressor Cells
MMP	Matrix Metalloproteinase

NCI	National Cancer Institute
NSCLC	Non Small Cell Lung Cancer
ORR	Objectiv Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD-1	Programmed Death 1
PD-L1	Programmed Death Ligand-1
PFS	Progression-free Survival
Q2W	Once every 2 weeks
RR	Respiratory Rate
RT	Radiotherapy
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WOCBP	Women of childbearing potential

16.0 APPENDICES

16.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

16.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

16.3 Response Evaluation Criteria in Solid Tumors

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

16.3.1 Measurability of tumor at baseline

DEFINITIONS
At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Nontarget Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

16.3.2 Target lesions: specifications by methods of measurements

Measurement of Lesions
All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

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

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether noncontrast CT or MRI (enhanced or nonenhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions

on a different modality and interpretation of nontarget disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

16.3.3 Tumor response evaluation

16.3.3.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

16.3.3.2 Baseline documentation of target and nontarget lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions.

Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

16.3.3.3 Response criteria

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions
  Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline.
  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  The appearance of one or more new lesions is also considered progression.
- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each

subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all nontarget lesions and (if applicable) normalization of tumor marker level
  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions
  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall

progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease.
The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions
The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

16.3.3.4 Evaluation of response

Timepoint Response (Overall Response)
It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore nontarget) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Nontarget Lesions)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR= complete response; NE= not evaluable; PD = progressive disease;
PR= partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Nontarget Lesions Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR= complete response; NE= not evaluable; PD = progressive disease.
[a] "Non-CR/non-PD" is preferred over "stable disease" for nontarget disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an

assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more nontarget lesions are not assessed, the response for nontarget lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the nontarget response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR= complete response; NE= not evaluable; PD = progressive disease; PR = partial response;

SD= stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease as shown in Table 1, Table 2, and Table 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or nontarget lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or nontarget lesion.

16.4 Immune-modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed that account for the possible appearance of new lesions.

Immune-modified Response Evaluation Criteria in Solid Tumors (irRECIST) is derived from RECIST, Version 1.1 (v1.1) conventions[1,2,3] and immune-related response criteria[3,4,5] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Immune-Modified RECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	Immune-Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST= Response Evaluation Criteria in Solid Tumors.

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1 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) Eur J Cancer 2009;45:228−47.
2 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti−PD-L1 antibody in cancer. N Engl J Med 2012;366:2443−54.
3 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immunetherapy activity in solid tumors: immune-related response criteria Clin Can Res 2009;15:7412−20.
4 Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. J Immunother Can 2014;2:17.
5 Nishino M, Giobbie-Hurder A, Gargano M et al. Developing a common language for tumor response to immunotherapy: immune-reated response criteria using unidimensional measurements. Clin Can Res 2013;19:3936−43.

16.4.1 Definitions of measurable/non-measurable lesions

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression.

16.4.1.1 Measurable lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)

- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

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

16.4.1.2 Non-measurable lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

16.4.1.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions
Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic−blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

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

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

Lesions with Prior Local Treatment
Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated

progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

16.4.2 Tumor response evaluation

16.4.2.1 Definitions of target/non-target lesions

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non−lymph node lesions must be ≥ 10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

16.4.2.2 Calculation of sum of the diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of immune-modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis

of a new lymph node lesion ≥ 15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter ≥ 15 mm).

The appearance of new lymph nodes with diameter < 10 mm should not be considered pathological and not considered a new lesion.

16.4.2.3 Response criteria

Timepoint Response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

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

Note: The appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by ≥ 20% when compared with the sum of the diameters at nadir.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Immune-Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation
When no imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 1 Immune-Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Immune-Modified RECIST Timepoint Response
− 100% from baseline [b]	CR	CR
− 100% from baseline [b]	Non-CR or not all evaluated	PR
≤ − 30% from baseline	Any	PR
> − 30% to < +20%	Any	SD
Not all evaluated	Any	NE
≥ + 20%from nadir SLD	Any	PD

CR= complete response; NE= not evaluable; PD = progressive disease; PR = partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of the longest diameter.
[a] Percent change in sum of the diameters (including measurable new lesions when present).
[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

16.5 Methods of contraception

At a minimum, subjects must agree to use one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

For WOCBP

Highly effective methods of birth control include the following:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
   - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6. Intrauterine hormone-releasing system (IUS).
7. Complete abstinence
   - Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.
   - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
   - It is not necessary to use any other method of contraception when complete abstinence is elected.
   - Subjects who choose complete abstinence must continue to have pregnancy tests.

- Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
- The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

"MALE SUBJECTS WITH PARTNERS WHO ARE WOCBP:

Are required to use condoms, in addition to the requirement for their female partners who are WOCBP to use a highly effective method of contraception listed above."

UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicide only
4. Lactation amenorrhea method (LAM)

17.0 SIGNATURES

17.1 Sponsor's Representative

TYPED NAME	Stein Kaasa, MD PhD
TITLE	Head of Department
SIGNATURE	
DATE SIGNED	

17.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 8.2 – Serious Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	Jon Amund Kyte, MD PhD
TITLE	Principal investigator
SIGNATURE	
DATE SIGNED	

TYPED NAME	Åse Bratland, MD PhD
TITLE	Principal investigator
SIGNATURE	
DATE SIGNED	