TITLE: Phase I/II trial of anti-PD-1 checkpoint inhibitor nivolumab and 177Lu-DOTA0-Tyr3-Octreotatefor Patients with Extensive-Stage Small Cell Lung Cancer

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Study Drugs: Nivolumab, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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1.0 PRÉCIS

Background

- Small cell lung cancer (SCLC), which accounts up to 15% of all new cases of lung cancer, is a lethal cancer with a poor prognosis. About 60% of patients present with extensive-stage disease.
- The mainstay of treatment for extensive-stage SCLC (ES-SCLC) is systemic chemotherapy comprising platinum and etoposide. Despite initial sensitivity to chemotherapy, patients with ES-SCLC relapse quickly and their tumors become refractory to treatment within months. Novel systemic treatment options are needed for this highly aggressive cancer.
- Somatostatin receptors (SSTR) are expressed in neuroendocrine tumors (NETs) including SCLC. Peptide receptor radionuclide therapy (PRRT) utilizes radiolabeled SSTR2 analogs to treat NETs. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) is a novel ^{177}Lutetium-labeled somatostatin analog. Lutathera is under investigation in a number of different NETs and has an established safety profile.
- The clinical efficacy of immune checkpoint blockade targeting the programmed death 1 (PD-1) pathway has been shown in various cancers including SCLC. Nivolumab is a fully human IgG4 monoclonal antibody that targets PD-1. Preliminary data from studies of nivolumab monotherapy or nivolumab/ipilimumab combination therapy show activity and durable responses in patients with progressive SCLC.
- Given the positive effects of radiation on immunogenic response (e.g. release of tumor antigens, induction of chemokines promoting the recruitment of T cells into the tumor, upregulation of MHC class I proteins and costimulatory molecules on tumor cells), we hypothesize that Lutathera and nivolumab will interact synergistically to provide increased therapeutic activity in patients with ES-SCLC.

Primary objectives

- The primary objective of the **phase I portion** of the study is to determine the recommended phase II dose (RP2D) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate when given in combination with anti-PD-1 checkpoint inhibitor nivolumab in patients with small-cell lung cancer or advanced or inoperable grade I-II pulmonary NETs.

- The primary objective of the randomized **phase II portion** of the study is to compare the progression-free survival (PFS) in patients with ES-SCLC who were not progressing to first-line treatment with platinum-based therapy, after receiving combination treatment of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab as a maintenance therapy versus observation.

Secondary objectives

- To characterize the safety profile of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in combination with nivolumab. [Applicable to both phase 1 and 2 portions]
- In patients who were not progressing before initiating combination therapy: [applicable to the phase 2 portion]

- To assess the disease control rate (DCR) and objective response rate (ORR) after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus nivolumab.
- To assess overall survival (OS).
- To assess whether the metabolic response seen on a NETSPOT® PET scan obtained on cycle 2 day 1 will predict response to study treatment.

Eligibility

Abbreviated Eligibility Criteria

1 For the phase I part, patients must have cytologically or histologically confirmed relapsed or refractory extensive-disease small-cell lung cancer (ES-SCLC) or non-progressing ES-SCLC after first line chemotherapy, or advanced or inoperable grade I-II pulmonary NETs.

2 For the randomized phase II part, patients must have cytologically or histologically confirmed ES-SCLC and must not have progressed after first line platinum-based chemotherapy regimen before randomization.

3 Toxicities of prior therapy must be resolved to grade 1 or less as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4 Patients with tumor tissue uptake during NETSPOT® PET that is equal to or higher than that in normal hepatic tissue (grade ≥2) will be eligible. It is recommended that NETSPOT® PET be obtained before initiation of chemotherapy, but NETSPOT® PET obtained during or after completion of chemotherapy could be used for screening purpose. Only for the phase I portion, at the discretion of the principal investigator, patients with SCLC whose tumors have lower levels of uptake than liver during NETSPOT® PET may be eligible for the study.

5 Patients with a history of autoimmune disease or other diseases requiring systemic glucocorticoid or immunosuppressive therapy, previous therapy with T-cell modulating antibodies (including anti-CTLA-4, anti-PD-1, anti-PD-L1), human immunodeficiency virus (HIV) infection, or active hepatitis B or C virus infection will be excluded.

6 Subjects with symptomatic brain metastases will be excluded. However, subjects who have had treatment for their brain metastasis and are asymptomatic without steroid therapy for at least 2 weeks may be enrolled.

7 ECOG performance status of 0-1.

8 Adequate organ and bone marrow function (hemoglobin > 9 g/dL; absolute neutrophil count > 1.5 x 10^{9}/L; platelet counts > 100 x 10^{9}/L; serum bilirubin < 2 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN or < 5 x ULN if liver metastases; calculated creatinine clearance > 50 mL/min).

9 Life expectancy of at least 3 months.

10 Age > 18 years.

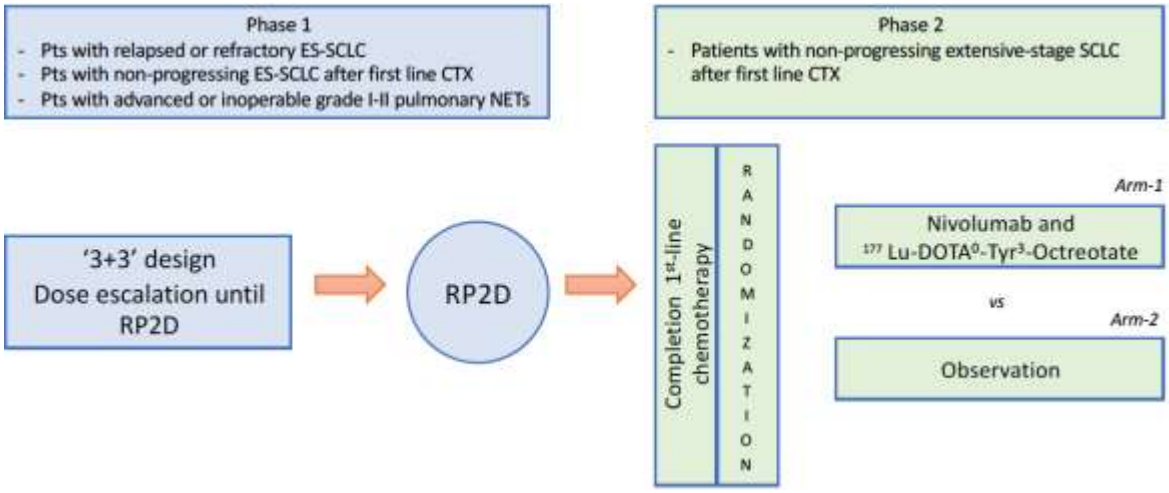
11 Ability to understand and willingness to sign a written informed consent document.

12 Patients who received prior anti-tumoral radionuclide therapy (with unsealed sources) are not eligible for the study.

Design

- Open-label, prospective phase I/II trial
- A randomized phase II study

Schema



CTX: chemotherapy

ES-SCLC: Extensive-stage small cell lung cancer

Pts: Patients

RP2D: Recommended phase II dose

2.0 BACKGROUND AND RATIONALE

2.1 Small cell lung cancer (SCLC)

2.1.1 Overview of SCLC

Neuroendocrine tumors (NETs) are a heterogeneous group of solid tumors that arise from neuroendocrine cells throughout the body. Neuroendocrine tumors of the lung represent a wide spectrum of disease from low-grade typical carcinoid and intermediate-grade atypical carcinoid to high-grade groups of large-cell neuroendocrine carcinoma and small-cell carcinoma (SCLC) [1]. SCLC makes up about 15% of all lung cancers and about 60% of patients with SCLC present with ES-SCLC [2]. Patients with SCLC often present with rapid onset of symptoms and significant symptoms due to rapid intrathoracic tumor growth, distant metastasis, paraneoplastic syndromes, or a combination of these features [3]. Patients with SCLC have a poor prognosis. The 5-year survival rate for limited-stage SCLC is 12%, and 1.6% for ES-SCLC [4, 5].

2.1.2 Treatment for SCLC

Treatment options for SCLC are limited. Platinum-based chemotherapy regimens have been the standard of care for a long time [6]. While the combination of platinum-based chemotherapy and thoracic radiotherapy (RT) for limited-stage SCLC produces response rates close to 90%, the duration of response is relative short, and most patients relapse after completion of treatment, although approximately 20% of patients can be cured with concomitant chemo-radiation [7, 8]. For patients with ES-SCLC, chemotherapy is the mainstay of treatment, but objective response rates (ORRs) are lower at 45-60%, with infrequent complete responses and median PFS and OS of around 5 months and 10 months, respectively [9, 10]. Second-line chemotherapy for the treatment of relapsed SCLC is less effective than the initial treatment. Topotecan is the only drug that was approved by the US Food and Drug Administration (FDA) for the treatment of relapsed SCLC in 1996 [11]. Topotecan yields objective response rates of 20-24% [12, 13]. The response rate in patients refractory to prior chemotherapy (6%) is lower than (37%) in those sensitive to first-line chemotherapy [12]. Prognosis for patients with relapsed SCLC is grim with a median overall survival of 5.4 months [12]. There is an urgent need to develop more effective therapies for patients with SCLC.

2.2 Nivolumab

Recent additions to the therapeutic armamentarium for cancer treatment are the immune checkpoint inhibitors. The programmed death-1 (PD-1)/programmed death-1 ligand (PD-L1) pathway is implicated in the mechanisms whereby tumors limit the host immune response [14]. Nivolumab is a humanized anti-PD-1 monoclonal antibody that inhibits the binding of PD-L1 to PD-1 and as a result, potentiates antitumor immune responses[15]. Emerging evidence indicates that patients whose tumors overexpress PD-L1 have improved clinical outcomes with anti-PD-L1 antibody therapy [16]. Nivolumab has been approved by the FDA in patients with melanoma, NSCLC, renal cell carcinoma, Hodgkin’s lymphoma, head and neck cancer, and urothelial carcinoma[17].

2.2.1 Non-clinical studies of Nivolumab (from the Nivolumab Investigator's Brochure, version 15, June, 2016)

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2.2.2 Clinical studies of Nivolumab

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2.3 ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

For grade 1-2 NETs of pulmonary origin, a new treatment modality is peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs [21]. In PRRT, octreotide, a somatostatin analog, is coupled with a radionuclide. Since most NETs overexpress somatostatin receptors, they are targets for radionuclide coupled to octreotide [22]. Tumors expressing somatostatin receptors can be readily visualized using radiolabeled somatostatin analogs such as [^{111}In-DTPA^{0}]-octreotide (OctreoScan®; Mallinckrodt, St Louis, MO) [22] or ^{68}Gallium DOTATATE (NETSPOT®) [23]. NETSPOT® is a significant improvement over OctreoScan®, with a higher sensitivity, rapid image acquisition, higher spatial resolution, higher affinity to SSTR2, less effective dose per Mbq injected, and lower radiation exposure. Several radiolabeled somatostatin analogs have been introduced with therapeutic purposes, and one of them is ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, a novel somatostatin analog DOTATATE, labeled with the ɣ (gamma) and beta particle-emitting radioisotope ^{177}Lutetium [24].

2.3.1 Non-clinical studies of Lutathera (from the Lutathera Investigator's Brochure)

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[redacted]

2.3.2 Clinical studies of Lutathera (from the Lutathera Investigator's Brochure, Version 15, June 2015)

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2.4 Rationale for the combination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab

The role of combination therapy using radiotherapy and cancer immunotherapy is emerging in cancer treatment [40]. Radiation therapy can cause the release of tumor antigens and convert tumors into an *in situ* vaccine [41]. It can also induce the expression of chemokines promoting the recruitment of T cells into the tumor and increase the expression of death receptors, MHC class I proteins, and costimulatory molecules on tumor cells [41]. These responses augment antitumor effects of anti-PD-1 monoclonal antibody. Previous work also reported on radiotherapy resulting in a significant upregulation of immune effectors and cancer-testis antigens and concomitant downregulation of immune suppressors after radiotherapy in sarcomas[42]. Clinically, this synergistic effect has been observed as an abscopal effect that refers to a regression of non-irradiated lesions in patients treated with concurrent radiotherapy and immunotherapy [43]. The synergistic effects of radiation and checkpoint inhibitor therapy have also been tested in various studies as in colon cancer and glioma, where the synergistic effect of combination of anti-PD-1 or PD-L1 antibody and external beam radiation was shown with regard to tumor control and increase in PD-L1 antigen expression after radiation [44, 45]. In light of the shared features of SCLC with neuroendocrine tumors, the use of checkpoint inhibitors in SCLC, and the positive effects of radiation on immunogenic response, we believe the combination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in combination with nivolumab might lead to powerful positive interactions. Since there is no

effective maintenance therapy for patients with ES-SCLC, this population is suitable for our investigational phase I/II study. Here we propose a phase I/II study of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab in patients with ES-SCLC to assess the safety and efficacy of the combination. Since SSTR2 is moderately overexpressed in many tumors (e.g. breast, lymphoma, glioma, prostate, meningioma), this phase I/II trial might be pivotal to subsequently explore the combination of PRRT and checkpoint inhibitors treatment in a broader variety of tumors.

3.0 STUDY HYPOTHESIS AND OBJECTIVES

3.1 Hypothesis

We hypothesize that the combination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab is safe and tolerable, and provides PFS benefit compared to observation alone in the maintenance setting in patients with ES-SCLC and no disease progression after first-line platinum-based chemotherapy.

3.2 Primary objectives

3.2.1 The primary objective of the phase I portion of the study is to determine the RP2D of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate when given in combination with anti-PD-1 checkpoint inhibitor nivolumab in patients with small-cell lung cancer or advanced or inoperable grade I-II pulmonary NETs.

3.2.2 The primary objective of the phase II portion of the study is to compare the PFS in patients with ES-SCLC who were not progressing to first-line treatment with platinum-based therapy, after receiving combination treatment of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab as a maintenance therapy versus observation.

3.3 Secondary objectives

3.3.1 To characterize the safety profile of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in combination with nivolumab. [Applicable to both phase 1 and 2 portions]

3.3.2 In patients who were not progressing before initiating combo therapy: [Applicable to the phase 2 portion]

- To assess DCR and ORR after treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate plus nivolumab.
- To assess OS
- To assess whether the metabolic response seen on a NETSPOT® PET scan obtained on cycle 2 day 1 will predict response to study treatment.

4.0 PATIENT ELIGIBILITY

4.1 Phase I

4.1.1 Inclusion Criteria

4.1.1.1 Patients must have cytologically or histologically confirmed relapsed or refractory extensive-disease small-cell lung cancer (ES-SCLC) or non-progressing ES-SCLC after first line chemotherapy, or advanced or inoperable grade I-II pulmonary NETs.

4.1.1.2 Patients with tumor tissue uptake during NETSPOT® PET that is equal to or higher than that in normal hepatic tissue (grade ≥2) will be eligible. At the discretion of the principal investigator, patients with SCLC whose tumors have lower levels of uptake than liver during NETSPOT® PET may be eligible for the study.

4.1.1.3 Toxicities of prior therapy must be resolved to grade 1 or less as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy.

4.1.1.4 Prior chemotherapy, radiotherapy or radiosurgery (including prophylactic cranial radiation and/or thoracic radiation) must have been completed at least 2 weeks prior to study treatment.

4.1.1.5 ECOG performance status of 0-1.

4.1.1.6 Adequate organ and bone marrow function (hemoglobin > 9 g/dL; absolute neutrophil count > 1.5 x 10^9/L; platelet counts > 100 x 10^9/L; serum bilirubin < 2 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN or < 5 x ULN if liver metastases; calculated creatinine clearance > 50 mL/min).

4.1.1.7 Life expectancy of at least 3 months.

4.1.1.8 Age > 18 years.

4.1.1.9 Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception for 23 weeks after the last dose of investigational drug. Men who are sexually active with WOCBP must use any contraceptive method(s) with a failure rate of less than 1% per year for 31 weeks after the last dose of investigational drug. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men) do not require contraception. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. See Section 4.3 for the definition of WOCBP.

4.1.1.10 Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropic [HCG]) within 24 hours prior to the start of the study drug.

4.1.1.11 Women must not be pregnant or breastfeeding.

4.1.1.12 Ability to understand and willingness to sign a written informed consent document.

4.1.2 Exclusion Criteria

4.1.2.1 Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

4.1.2.2 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

4.1.2.3 Subjects with symptomatic brain metastases will be excluded. However, subjects who have had treatment for their brain metastasis and are asymptomatic without steroid therapy for at least 2 weeks may be enrolled.

4.1.2.4 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

4.1.2.5 Treatment with investigational agents is prohibited from 30 days prior to the first dose of the study treatment, and throughout the study.

4.1.2.6 History of a previous malignancy within the last 2 years, with the exception of early stage cancers that are at very low risk of recurrence, such as non-melanoma skin cancer, papillary carcinoma of the thyroid, or carcinoma in situ of the prostate, cervix, or breast.

4.1.2.7 Patients with human immunodeficiency virus (HIV) infection, or active hepatitis B or C virus infection will be excluded.

4.1.2.8 Patients who received prior anti-tumoral radionuclide therapy (with unsealed sources) are not eligible for the study.

4.1.2.9 Prior major surgery within 12 weeks or prior major surgery from which the patient has not sufficiently recovered yet.

4.1.2.10 Logistical or psychological hindrance to participation in clinical research.

4.1.2.11 Uncontrolled or significant cardiovascular disease, including any of the following:

- Symptomatic congestive heart failure (≥New York Heart Association Classification Class II).
- Cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), or unstable angina.
- Uncontrolled hypertension or uncontrolled cardiac arrhythmia.

4.1.2.12 Any other medical condition that in the Investigator's opinion would not make the patient a good candidate for the study.

4.2 Phase II

4.2.1 Inclusion Criteria

4.2.1.1 Patients must have cytologically or histologically confirmed ES-SCLC and must not have progressed after first line platinum-based chemotherapy regimen before randomization.

4.2.1.2 Patients with tumor tissue uptake during NETSPOT® PET that is equal to or higher than that in normal hepatic tissue (grade ≥2) will be eligible. It is recommended that NETSPOT® PET be obtained before initiation of chemotherapy, but NETSPOT® PET obtained during or after completion of chemotherapy could be used for screening purpose.

4.2.1.3 Toxicities of prior therapy must be resolved to grade 1 or less as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 with the exception of alopecia and grade 2, prior platinum-therapy related neuropathy.

4.2.1.4 Prior radiotherapy or radiosurgery (including prophylactic cranial radiation and/or thoracic radiation) must have been completed at least 2 weeks prior to randomization.

4.2.1.5 For patients who do not receive radiotherapy after chemotherapy, the randomization must occur within 6 weeks of the last chemotherapy cycle. The study treatment must start within 2 weeks from randomization and no less than 2 weeks from last chemotherapy dose. For patients who receive radiotherapy (including prophylactic cranial radiation and/or thoracic radiation) after chemotherapy, the randomization must occur at least 8 weeks after completion of radiation therapy but within 12 weeks after completion of radiation therapy.

4.2.1.6 ECOG performance status of 0-1.

4.2.1.7 Adequate organ and bone marrow function (hemoglobin > 9 g/dL; absolute neutrophil count > 1.5 x 10^9/L; platelet counts > 100 x 10^9/L; serum bilirubin < 2 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN or < 5 x ULN if liver metastases; calculated creatinine clearance > 50 mL/min).

4.2.1.8 Life expectancy of at least 3 months.

4.2.1.9 Age > 18 years.

4.2.1.10 Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception for 23 weeks after the last dose of investigational drug. Men who are sexually active with WOCBP must use any contraceptive method(s) with a failure rate of less than 1% per year for 31 weeks after the last dose of investigational drug. Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men) do not require contraception. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. See Section 4.3 for the definition of WOCBP.

4.2.1.11 Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropic [HCG]) within 24 hours prior to the start of the study drug.

4.2.1.12 Women must not be pregnant or breastfeeding.

4.2.1.13 Ability to understand and willingness to sign a written informed consent document.

4.2.2 Exclusion Criteria

4.2.2.1 Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

4.2.2.2 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

4.2.2.3 Subjects with symptomatic brain metastases will be excluded from trial secondary to poor prognosis. However, subjects who have had treatment for their brain metastasis and whose brain disease is stable without steroid therapy for 2 weeks may be enrolled.

4.2.2.4 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

4.2.2.5 Treatment with investigational agents is prohibited from 30 days prior to the first dose of the study treatment, and throughout the study.

4.2.2.6 History of a previous malignancy within the last 2 years, with the exception of early stage cancers that are at very low risk of recurrence, such as non-melanoma skin cancer, papillary carcinoma of the thyroid, or carcinoma in situ of the prostate, cervix, or breast.

4.2.2.7 Patients with human immunodeficiency virus (HIV) infection, or active hepatitis B or C virus infection will be excluded.

4.2.2.8 Patients who received prior anti-tumoral radionuclide therapy (with unsealed sources) are not eligible for the study.

4.2.2.9 Prior major surgery within 12 weeks or prior major surgery from which the patient has not sufficiently recovered yet.

4.2.2.10 Logistical or psychological hindrance to participation in clinical research.

4.2.2.11 Uncontrolled or significant cardiovascular disease, including any of the following:

- Symptomatic congestive heart failure (≥New York Heart Association Classification Class II).
- Cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), or unstable angina.
- Uncontrolled hypertension or uncontrolled cardiac arrhythmia.

4.2.2.12 Any other medical condition that in the Investigator's opinion would not make the patient a good candidate for the study.

4.3 WOCBP/MOCBP

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In additional, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40 mIU/mL. Women treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used:

- 1-week minimum for vaginal hormonal products, (rings, creams, gels)

- 4-week minimum for transdermal products
- 8-week minimum for oral products.

Other parenteral products may require washout periods as long as 6 months.

Women of childbearing potential (WOCBP) must agree to follow instructions for acceptable contraception from the time of signing consent, and for 23 weeks after their last dose of protocol-indicated treatment.

Men not azoospermic who are sexually active with WOCBP must agree to follow instructions for acceptable contraception from the time of signing consent, and for 31 weeks after their last dose of protocol-indicated treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

5.1.1 Phase I

5.1.1.1 Dose Limiting Toxicity (DLT)

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs from the first dose of study treatment (Day 1, Cycle 1) up to the last day of the cycle (Day 57). To be considered as DLT, it must be related to the study drugs (attributions: possible, probable, and definite) while fulfilling one of the following criteria as per the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03:

- Toxicity grade 2 for platelets and any other grade 3 or 4 toxicity, excluding
    - Grade 3 diarrhea, nausea, or vomiting if it can be controlled with supportive therapy
    - Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic.
- Persistent (>21 days) non-hematologic grade 2 adverse events despite optimal medical management and treatment delay > 21 days
- Any other toxicity:
    - if worse than baseline value, documented, clinically relevant and/or unacceptable, and is judged to be a DLT by the investigators
    - if results in a protocol defined stopping criteria
    - if results in disruption of dosing schedule

Patients experiencing DLT will be monitored weekly until toxicity stabilization, and then every two weeks until normalization.

5.1.1.2 Dose Escalation and Treatment Duration

Treatment will be administered on an outpatient basis.

A standard dose-escalation phase I design will be used. Three subjects will be enrolled at each

dose level in the absence of DLT. Please find the details in the dose escalation table below.

Dose escalation table

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. • Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤2 out of 6 at highest DL	This is generally the recommended phase 2 dose. At least 6 patients must be treated at the recommended phase 2 dose.

Selection of the starting dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab is based on the results from previous clinical studies with each compound used as single agent and the fact that the combination has not been tested in clinical trials. The first dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be given two weeks after the first administration of nivolumab. Studies have shown that intravenous administration of amino acids has a renal protective effect [46]. An infusion of amino acids will be started 30 minutes before the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and last 4 hours (Table 3).

Patient Replacement

Three patients within a dose level must be observed for one cycle (56 days) before accrual to the next higher dose level may begin. If a patient is withdrawn from the study prior to completing 56 days of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level.

5.1.2 Phase II

The phase II portion will consist of patients with ES-SCLC who completed platinum based standard first-line chemotherapy (e.g. 4-6 cycles of platinum plus etoposide or irinotecan) without disease progression (responders plus stable disease) at the time of initiation of the combination therapy with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab. Eligible patients will then be randomly allocated in two arms: one will be treated with the combination of ^{177}Lu-DOTA^{0}-Tyr^{3}-

Octreotate and nivolumab, and the other arm will continue be followed (observation) after completion the standard chemotherapy treatment.

Randomization:

Patients who do not receive radiotherapy after chemotherapy

- The randomization must occur within 6 weeks of the last chemotherapy cycle.
- The study treatment must start within 2 weeks from randomization, but no less than 2 weeks from last dose of chemotherapy.

Patients who receive radiotherapy (including prophylactic cranial radiation and/or thoracic radiation) after chemotherapy

- Randomization must occur at least 8 weeks after completion of radiation therapy but within 12 weeks after completion of radiation therapy.

Randomization process:

- OnCore will be used as statistical center and the randomization algorithm will be developed by the study biostatistician.
- The project management department will be the first point of contact for assessment through email.

Courses are defined as 56 days of dosing. Nivolumab will be given until progressive disease, patient withdrawal, or toxicities. For patients randomized to the observation group, cross-over at the time of disease progression will be allowed, since the primary endpoint is PFS and not OS.

5.2 Drug Administration

5.2.1 ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be administered every 8 weeks. The first dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be given two weeks after the first administration of nivolumab. Each dose is infused over 30 minutes. On the day of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate infusion, an intravenous bolus of anti-emetics will be given (suggested options: ondansetron (8 mg), granisetron (3 mg), or tropisetron (5 mg)). Administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate may be given one day earlier or delayed up to 1 week due to holidays, inclement weather, conflicts, or similar reasons. Prednisone should be avoided as preventive anti-emetic treatment due to potential-negative effect on anti-PD-1 therapy. In case of nausea or vomiting despite the use of aforementioned anti-emetic, patients can be treated with other anti-emetic medications at the discretion of the treating physician.

Concurrent amino acids are given with each dose of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate since co-infusion of amino acids leads to a significant reduction (47%) in the mean radiation dose to the kidneys. The amino acid solution and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are administered in parallel by peripheral vein infusion.

Table 2. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Administration Schedule.

Preparation	Starting time (h)	Infusion Rate (ml/h)	Duration (h)
Granisetron 3 mg (or alternative)	0	Bolus	-
Amino acids: 1-2.2 L solution*	0	250 to 550**	4
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	0.5	50	0.5
Saline solution 25 mL – (two pump method)[1]	1	50	0.5

[1]When the two-pump method is used, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is pumped directly into the infusion line. The infusion line must be flushed with at least 25 ml of sodium chloride 9 mg/ml (0.9%) solution for injection after the infusion of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

* For specifications of the recommended commercial amino acid solution for coinfusion, please refer to the investigator brochure.

** The infusion rate may be reduced at the discretion of the investigator.

5.2.2 Nivolumab

Nivolumab will be administered once every 2 weeks until disease progression, patient withdrawal or toxicities. Nivolumab is administered intravenously and is administered first in combination studies. Wait 30 minutes before the next compound is administered (regardless of route of administration). Administer the infusion over 30 minutes (+/- 5 minutes) through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (polyethersulfone with pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Nivolumab infusions are compatible with PVC or polyolefin containers and infusion sets, and glass bottles. Flush the intravenous line at end of infusion with appropriate amount of diluent (15-20 ml) to ensure that the total dose is administered. Administration of nivolumab may be given one day earlier or delayed up to 1 week due to holidays, inclement weather, conflicts, or similar reasons. The timing of subsequent administrations is then adjusted to maintain a 14 days-interval.

5.3 Dose Delays/Dose Modifications and Management of Toxicities Associated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab

5.3.1 General Recommendations for Evaluation of Toxicities and Dose Delays/Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose delays or dose modifications should be made according to the system showing the greatest degree of toxicity. Once the patient has a dose reduction due to toxicity, the dose will not

be re-escalated. Dose delays and dose modifications will be made using the following recommendations. At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed AE is attributed to only one of the study drugs, while the patient continued to receive the drug not associated with the observed AE. For example, if the patient develops immune-related adverse events, nivolumab may be held following guidelines in section 5.3.5 while the patient continues to receive ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate. If the patient develops hematologic adverse events that are frequently associated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, but rarely associated with nivolumab (e.g. thrombocytopenia), ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate may be held while the patient continues on nivolumab. If the observed toxicity is attributable to both drugs, both drugs will be held.

Dose modifications for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate are permitted according to the table below.

Dose Level (DL)	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (IV)
Level 1	3.7 GBq (100 mCi) every 8 weeks
Level 2	7.4 GBq (200 mCi) every 8 weeks

No dose modifications are allowed for nivolumab.

5.3.2 Hematologic Toxicities

Table 3. General Recommendations for Dose Modifications and Management of Hematological Toxicities

Adverse Event or Observation	Management
ANC* ≥ 1,000/mm^3 AND Platelets** ≥ 75,000/mm^3 AND Hemoglobin*** ≥ 8 g/dL	Maintain dose
ANC < 1,000/mm^3 OR Platelets <75,000/mm^3 OR Hemoglobin <8 g/dL	On first occurrence, hold the drug(s) causing the toxicity up to 21 days until ANC ≥ 1,000/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 9 g/dL. The subinvestigator and/or PI will determine whether one or both drugs are responsible for an observed toxicity and will initiate appropriate medical therapy and no change in dose upon re-initiation.

	On second occurrence, hold the drug(s) causing the toxicity up to 21 days until ANC ≥ 1,000/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 9 g/dL. Treatment with ^{177}Lu-DOTA^0-Tyr^3-Octreotate may be restarted one dose level lower. Patient who have not recovered to ANC ≥ 1,000/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 9 g/dL after 21 days should be removed from the drug causing the toxicity.
Grade 4 hematologic AE	On first occurrence, hold the drug(s) causing the toxicity up to 21 days until ANC ≥ 1,000/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 9 g/dL. Treatment with ^{177}Lu-DOTA^0-Tyr^3-Octreotate may be restarted one dose level lower. On second occurrence, discontinue the drug(s) causing the toxicity. Follow patient until resolution and/or stabilization of toxicity. Patient who have not recovered to ANC ≥ 1,000/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 9 g/dL after 21 days should be removed from the drug causing the toxicity.

*ANC: Absolute neutrophil count. Growth factors to prevent neutropenia will not be administered prophylactically, but can be used during a drug hold to assist the recovery.

** Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤ 10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

*** Red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL or the patient is symptomatic. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org).

5.3.3 Non-hematologic Toxicities

- The management of general AEs not otherwise specified in the following sections should be as per **Table 5**.
- Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment. The time a given drug is held should not exceed 21 days.

Table 4. General Recommendations for Dose Modification and Management of Non-Hematological Toxicities

Observation	Management

Grade 1 non-hematologic AE	Maintain dose level.
Any grade 2 non-hematologic AE related to study drug(s) lasting >7 days despite maximal intervention	Hold study drug(s)** for up to 21 days until toxicity resolves to ≤ grade 1. Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate may be restarted one dose level lower.
Any ≥ grade 3 non-hematologic*	Hold study drug(s)** for up to 21 days until toxicity resolves to ≤ grade 1 or baseline. Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate may be restarted one dose level lower.
Grade 3 or 4 non-hematologic AE related to drugs* that does not resolve to grade 1 or less within 21 days despite maximum supportive care after treating patient at the lowest reduced DL.	Remove patient from study regimen.

* Excluding 1) Grade 3 fatigue/asthenia < 2 weeks in duration, or grade 3 asymptomatic electrolytes imbalance with optimal and continuing repletion that downgrades to grade 1 or better within 7 days after onset of the event; 2) Grade 3 asymptomatic increase in gamma glutamyl transferase (GGT).

** For patients on combination therapy, if the observed AE is specifically attributed to only 1 of the drugs, that drug may be held while the patient continues to receive the drug not associated with the observed AE. The time a given drug is held should not exceed 21 days.

5.3.4 Management of Infusion-Related Reactions

Table 5. Dose Modifications and Management of Infusion-Related Reactions

Observation	Management
Grade 1 or 2 AE	The infusion rate of study drug(s) may be decreased by 50% or temporarily interrupted until resolution of the event. Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. Consider premedication prior to subsequent doses.
Grade 3 or 4 AE	Discontinue study drug(s). Manage severe infusion-related reactions (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

5.3.5 Management of Immune-Related Toxicities

Treatment of immune-related adverse events (irAEs) should follow guidelines set forth in the following tables. Also, please refer to Appendix B for details.

Table 6. Dose Modification and Management of irAEs

Gastrointestinal irAEs (e.g. diarrhea, colitis)		
Observation	**Management**	**Follow-up**
Grade 1 AE	Continue nivolumab therapy. Consider symptomatic treatment (e.g. loperamide, hydration, electrolyte replacement).	Close monitoring for worsening symptoms. Educate patient to report worsening immediately. If worsens: Treat as Grade 2 or 3/4
Grade 2 AE	Delay nivolumab therapy. Symptomatic treatment.	If improves to Grade 1: Resume nivolumab therapy. If no improvement within 5-7 days or recur: Consider starting IV methylprednisolone 0.5-1.0 mg/kg/day or oral equivalent. Once improving, taper steroids over ≥1 month and consider prophylactic antimicrobials for opportunistic infections, and consider resuming nivolumab. If the event is not responsive within 3-5 days or worsens despite steroid: Treat as Grade 3/4.
Grade 3 to 4 AE	Discontinue nivolumab therapy. 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent. Consider urgent GI consult and imaging and/or colonoscopy as appropriate.	Once improving, taper steroids over ≥ 1 month and consider prophylactic antimicrobials for opportunistic infections. If still no improvement within 3-5 days or recurs after improvement despite steroid: consider adding further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks if no contraindication). **Caution**: Consider GI

		consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. Infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Observation	**Management**	**Follow-up**
Grade 1-2 AE	Symptomatic therapy (e.g. oral antihistamines, topical steroids). Continue nivolumab therapy.	If persists > 1-2 weeks or recurs: Consider delaying nivolumab. Consider skin biopsy. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over ≥ 1month, consider prophylactic antimicrobials for opportunistic infections, and resume nivolumab. If worsens: Treat as Grade 3-4.
Grade 3-4 AE	Delay or discontinue nivolumab therapy. 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent. Consider dermatology consult and/or skin biopsy.	If improves to Grade 1: taper steroids over ≥ 1 month and consider prophylactic antimicrobials for opportunistic infections and consider resuming nivolumab.

Pulmonary irAEs		
Observation	**Management**	**Follow-up**
Grade 1 AE	Consider delay of nivolumab therapy. Monitor for symptoms at least every 2-3 days.	Re-image at least every 3 weeks. If worsens: Treat as Grade 2 or Grade 3-4.

	Consider Pulmonary and Infectious Disease consults.	
Grade 2 AE	Delay nivolumab therapy. Consider Pulmonary and Infectious Disease consults. Monitor symptoms daily, consider hospitalization. 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1-3 days. If improves: When symptoms return to near baseline, taper steroids over ≥1 month, resume nivolumab therapy, and consider prophylactic antimicrobials. If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 or 4 AE	Discontinue nivolumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic microbials for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improves to baseline: Taper steroids over at least 6 weeks. If not improving within 48 hours or worsening: Add additional immunosuppression (e.g. infliximab, cyclosporine, tacrolimus, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil).

Hepatic irAEs		
Observation	**Management**	**Follow-up**
Grade 1 AE	Continue nivolumab therapy.	Continue liver function monitoring. If worsens: Treat as Grade 2 or 3-4.
Grade 2 AE	Delay nivolumab therapy. Regular and frequent checking (e.g. every 3 days) of LFTs until elevations of these are improving or resolved.	If returns to baseline: Resume routine monitoring, resume nivolumab therapy.

		If elevations persist > 5-7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or baseline, taper steroids over ≥ 1 month, consider prophylactic antimicrobials for opportunistic infections, and resume nivolumab therapy.
Grade 3 to 4 AE	Discontinue nivolumab therapy* Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** Add prophylactic antimicrobials for opportunistic infections. Consult gastroenterologist.	If returns to Grade 2 or better: Taper steroids over ≥ 1 month. If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

*Nivolumab therapy may be delayed rather than discontinued if AST/ALT <= 8 x ULN and Total bilirubin <= 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH elevation	Continue nivolumab therapy. If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult.	
Symptomatic endocrinopathy	Evaluate endocrine function. Consider pituitary scan.	If improves (with or without hormone replacement): Taper steroids over ≥1 month and consider prophylactic antimicrobials for opportunistic infections. Resume nivolumab therapy.

	Symptomatic with abnormal lab / pituitary scan: Delay nivolumab therapy. 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent. Initiate appropriate hormone therapy. No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness	Delay or discontinue nivolumab therapy. Rule out sepsis. Stress dose of IV steroids with mineralocorticoid activity. IV fluids. Consult endocrinologist. If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy.	

Renal irAEs		
Observation	**Management**	**Follow-up**
Grade 1 AE	Continue nivolumab therapy. Monitor creatinine weekly.	If returns to baseline: resume routine creatinine monitoring per protocol. If worsens: Treat as Grade 2 or 3/4.
Grade 2-3 AE	Delay nivolumab therapy. Regular and frequent checking of Creatinine (e.g. every 2-3 days) until Creatinine elevation is improving or resolved. 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent. Consider renal biopsy with nephrology consult.	If returns to grade 1: Taper steroids over ≥ 1 month, consider prophylactic antimicrobials for opportunistic infections, and resume nivolumab therapy and routine creatinine monitoring per protocol. If elevations persist > 7 days or worsen: Treat as Grade 4.

Grade 4 AE	Discontinue nivolumab therapy. Regular and frequent checking of Creatinine until Creatinine elevation is improving or resolved. 1 to 2 mg/kg/day methylprednisolone iv or iv equivalent. Consult nephrologist. Consider renal biopsy.	If returns to Grade 1: Taper steroids over ≥1 month, consider prophylactic antimicrobials for opportunistic infections.

Neurological irAEs		
Observation	**Management**	**Follow-up**
Grade 1 AE	Continue nivolumab therapy.	Continue to monitor the patient. If worsens: Treat as Grade 2 or 3/4.
Grade 2 AE	Delay nivolumab therapy. Treat symptoms per local guidelines. Consider 0.5 to 1 mg/kg/day methylprednisolone iv or oral equivalent.	If improves to baseline or grade 1: Resume nivolumab therapy per protocol when improved to baseline. If worsens: Treat as Grade 3-4.
Grade 3-4 AE	Discontinue nivolumab therapy. Obtain neurology consult. Treat symptoms per local guidelines. 1 to 2 mg/kg/day methylprednisolone IV or equivalent. Add prophylactic antibiotics for opportunistic infections.	If improves to grade 2: Taper steroids over ≥1 month. If worsens or atypical presentation: consider IVIG or other immunosuppressive therapies per local guidelines.

<table>
<tr><th colspan="3">Other irAEs</th></tr>
<tr><th>Observation</th><th>Dose Modifications</th><th>Toxicity management</th></tr>
<tr><td>Grade 1 AE</td><td>Continue nivolumab therapy.

Consider appropriate symptomatic treatment.</td><td rowspan="3">Subjects should be evaluated to identify any alternative etiology.

Symptomatic and/or topical therapy should be considered for low grade events.

Systemic corticosteroids should be considered for a persistent low-grade event or for a more severe event. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

More potent immunosuppressive agents should be considered for events not responding to systemic steroids (e.g., infliximab, mycophenolate, etc.).

Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient.</td></tr>
<tr><td>Grade 2 AE</td><td>Hold nivolumab until grade 2 resolution to ≤ grade 1.

If toxicity worsens, then treat as grade 3 or grade 4.

If toxicity improves to baseline, then consider restarting nivolumab.</td></tr>
<tr><td>Grade 3 AE**</td><td>Depending on the individual toxicity, may permanently discontinue nivolumab*</td></tr>
</table>

Grade 4 AE**	Permanently discontinue nivolumab.	

* In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity, permanently discontinue study drug/study regimen for the following conditions: 1) Inability to reduce corticorsteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen, 2) Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.

** For Grade 3 and above asymptomatic amylase or lipase levels, hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen

Abbreviations: ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, irAE=immune-related adverse event, IV=intravenous, LLN=lower limit of normal, MRI=magnetic resonance imaging, NSAIDs=nonsteroidal anti-inflammatory drugs, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal, IVIG=intravenous immunoglobulins, CPK=creatine phosphokinase.

5.4 Concomitant Medications/Treatments

Concomitant use of chemotherapy or investigational agents are not allowed. Palliative radiation to limited areas is allowed during the study, unless this is required because of progression of the disease.

5.5 Off-treatment criteria

Treatment may continue until one of the following criteria applies:

- Disease progression and investigator determination that the subject is no longer benefiting from study treatment*
- Any AE that meets criteria for discontinuation as defined in section 5.3.
- Patient decides to withdraw from the study.
- General or specific changes in the patient's condition render the patient unfit for further treatment in the judgment of the investigator.
- Patient is non-compliant with the protocol guidelines.

* Patients are allowed to stay on treatment beyond progression if the investigator thinks that the patient is still benefiting from the treatment.

5.6 Off-study criteria

- Death
- Patient decides to withdraw consent from the study.
- Lost to follow-up

- Completed study follow-up period
- Investigator discretion

5.7 Duration of Follow-Up

Patients will be followed either with clinic visits or phone interviews yearly for two years. Patients removed from treatment for unacceptable adverse event(s) will be followed clinically until resolution or stabilization of the adverse event, and then via clinic visits or phone interviews yearly for two years.

The following information will be collected:

- Date of follow up
- Is patient dead or alive?
- If dead, document exact date of death.
- Further treatment(s), if any
- Document date of disease progression

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Subjects who meet all eligibility criteria will be enrolled in the study. Assessments performed exclusively to determine eligibility for this study will be done after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. All screening procedures must be performed within 4 weeks prior to starting study drugs, unless otherwise stated. The screening procedures include:

- Complete history and physical examination including vital signs, height, weight and ECOG performance score (see appendix C).
- Baseline imaging studies: Patients should have a baseline radiographical evaluation with computed tomography (CT) scan of the chest/abdomen/pelvis, MRI or CT of the brain, and FDG-PET (skull base to mid-thigh). Two NETSPOT® PET scans will be performed, the first one within 4 weeks before the start of chemotherapy (preferable) or as soon as possible after initiation of chemotherapy. This scan will be used to evaluate SSTR2 expression and the patient's eligibility for the study. The second NETSPOT® PET scan will be conducted as far as possible from the end of chemotherapy (ideally within 1 week before the start of study treatment). This scan will be used for exploratory analysis on eventual SSTR2 expression modification with chemotherapy. If a patient presents after completion of chemotherapy and did not have a NETSPOT® PET scan performed before or during chemotherapy, a NETSPOT® PET scan will be obtained to determine the patient's eligibility. The participating centers of the proposed study will follow the approved reconstitution and quality control procedures for [^{68}Ga]-DOTATE, and will use the qualified Ge-68/Ga-68 generator. Outside imaging studies will be accepted at the discretion of the PI.
- Electrocardiogram (EKG)

- Laboratory evaluation (baseline tests to be obtained within two weeks prior to starting treatment unless otherwise noted)
    - Hematological Profile: Complete blood count (CBC) with differential and platelet count, prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT).
    - Biochemical Profile: Sodium, potassium, calcium, phosphorous, magnesium, blood urea nitrogen (BUN), creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactic acid dehydrogenase (LDH), bilirubin, albumin.
    - Baseline glomerular filtration rate (GFR) calculation.
    - Serum or urine beta-hCG for female patients of childbearing age within 24 hours prior to the start of study drug.
    - Viral Markers: HBsAg (hepatitis B surface antigen), anti-HCV antibody, anti-HIV antibody within 3 months prior to starting treatment.
    - Amylase, lipase, thyroid function test (TSH, free T3, free T4).

6.2 Procedures During Treatment

Patients receiving study treatment will be followed every 2 weeks and the following will be done (unless otherwise indicated).

- History and physical exam (± 3 days).
- Laboratory evaluation (± 3 days): Hematologic profile (CBC with differential). Biochemical profile. Does not need to repeat for C1D1 if performed within 7 days.
- Thyroid function testing will be done every cycle on day 1 (± 3 days) and day 29 (± 3 days) for subjects receiving nivolumab. Does not need to repeat on C1D1.
- Tumor imaging will be performed every 8 weeks (± 7 days).
- NETSPOT® PET scan on cycle 2 day 1 (± 3 days) to assess the metabolic response.
- Serum or urine beta-hCG for female patients of childbearing age within 24 hours prior to the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

Patients randomized to observation will be followed every 4 weeks and the following will be done.

- History and physical exam (± 3 days).
- Laboratory evaluation (± 3 days): Hematologic and biochemical profile. Laboratory evaluation can be performed within 3 days prior to clinic visit.
- Tumor imaging will be performed every 8 weeks (± 7 days).

After 30 days (± 7 days) from treatment termination, the following will be obtained if the patient is available:

- History and physical exam.
- Laboratory evaluation: Hematologic and biochemical profile. Thyroid function testing.

6.3 Follow-up

Patients will be followed either with clinic visits or phone interviews yearly for two years. Patients removed from treatment for unacceptable adverse event(s) will be followed clinically until

resolution or stabilization of the adverse event, and then via clinic visits or phone interviews yearly for two years.

The following information will be collected:

- Date of follow up
- Is patient dead or alive?
- If dead, document exact date of death.
- Further treatment(s), if any
- Document date of disease progression
- Long-term myelosuppression, myelodysplasia, and occurrence of secondary malignancies.

6.4 Study Calendar

Please refer to **Appendix D**.

7.0 Measurement of Effect

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [47]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST version 1.1 criteria.

7.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab.

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

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

7.1.2 Disease Parameters

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

Note: Tumor lesions that are located in a previously irradiated area might or might not be considered measurable at the discretion of the PI.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in 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.

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

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

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

Conventional CT and MRI: CT and MRI - CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. For this study helical multidetector CT will be performed with cuts of 5 mm in slice thickness for chest, abdomen and pelvis lesions and 2-3 mm thickness for head and neck lesions. For consistency, it is recommended that investigators use the same imaging modality for follow-up of tumors for a given patient.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

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

FDG-PET: New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up may be a sign of progressive disease. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease (PD). If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site. If so, the date of PD will be the date of the initial abnormal FDG-PET scan. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Complete Response (CR): Disappearance of all target lesions. There can be no appearance of new lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of target lesions, taking as reference the baseline sum diameters. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 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 diameters while on study.

7.1.4.2 Evaluation of Non-Target Lesions

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

7.1.4.3 Evaluation of Best Overall Response

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

Table 7. Evaluation of patients with measureable disease.

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.			

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: 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 the objective progression even after discontinuation of treatment.

Table 8. Evaluation of patients with non-measureable disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

7.1.5 Duration of Response

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

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

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

7.1.6 Progression-Free Survival

PFS is defined as the duration of time from randomization to time of progression or death, whichever occurs first.

7.1.7 Overall Survival

Overall survival is defined as the duration of time from randomization to death from any cause.

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

AEs should be reported up to 30 days following the last dose of study drug. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

8.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. The term 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator

brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious Adverse Events

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

- Death.
- A life-threatening adverse drug experience.
- NOTE: The term “life-threatening” in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization, excluding hospitalizations done to facilitate research studies or for non-medical reasons (to facilitate completion of protocol-directed requirements, i.e. biopsy, imaging, desensitization for platinum).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such 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)**
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug is a serious adverse event.

*Dr. Giuseppe Giaccone is the sponsor of this trial.

**Potential Drug Induced Liver Injury

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 potential drug induced liver injury is defined as:

1) 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 AST/ALT 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.

8.1.5 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE v4.0 is available at http://ctep.cancer.gov/reporting/ctc.html

Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE is *doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

8.3 Reporting Requirements for Adverse Events

Participating investigators (all sites) must report all serious adverse events to the Sponsor-Investigator within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution. The Sponsor-Investigator can be contacted at Giuseppe Giaccone, E-mail: gg496@georgetown.edu, phone: 202-687-7072 with CC to Multi-Site-AEReports@georgetown.edu and CC to sub-investigator Chul Kim, E-mail: chul.kim@gunet.georgetown.edu.

The Sponsor-Investigator will review the SAE and report the event to the FDA, external collaborator(s), IND manufacturer, and IRB as applicable as described below.

It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that all serious adverse events that occur on the study (e.g. all SAEs that occur at each enrolling institution) are reported to all participating sites.

*After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be reported.

**After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or last observation follow-up visit or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events will continue to be reported until 90 days after the last dose of study treatment or last observation follow-up visit or until initiation of new systemic anti-cancer therapy, whichever occurs first.

8.3.1 Expedited IRB Reporting

The institutional officials must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR). UPRs are defined as any problem or event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.3.2 FDA Reporting Criteria

8.3.2.1 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)

The Sponsor will notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.

The Sponsor is also responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH

5600 Fishers Lane

Rockville, MD 20852-9787

Fax: 1-800-FDA-0178 (1-800-332-0178)

http://www.accessdata.fda.gov/scripts/medwatch/

8.3.2.2 FDA Annual Reports (Refer to 21 CFR 312.32)

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

8.3.3 IND Manufacturer Reporting

8.3.3.1 Reporting of Adverse Events (SAEs) to Advanced Accelerator Applications (AAA)

A copy of the MedWatch/AdEERs report must be faxed to AAA at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AAA at the same time.

* Send SAE report and accompanying cover page by way of email to Pharmacovigilance@adacap.com (email is the preferred method)

OR

* Send SAE report and accompanying cover page by way of fax to line: 1-212-235-2381

8.3.3.2 Reporting of Adverse Events (SAEs) to Bristol-Myers Squibb (BMS)

See Appendix E for mandatory adverse event reporting information. All serious adverse events must be reported to BMS Worldwide Safety.

9.0 DRUG INFORMATION

9.1 ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

9.1.1 Investigational Drug Product: ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate is a radiopharmaceutical solution for infusion supplied as a ready-to-use product. No manipulation of the product in needed at the clinical site. The only Quality Control (QC) tests that must be performed at the clinical site are; 1) confirm correct product certificate; 2) determine total radioactivity; 3) confirm visual appearance. Since 177Lu-DOTA0-Tyr3-Octreotate is manufactured in centralized GMP facilities, the majority of required QC tests are performed before product shipment. A batch release certificate of the product will be sent to the investigational centers. This batch release certificate is provided by the Qualified Person (QP) of the manufacturing site to ensure that the product is suitable for administration and that it meets the specifications indicated in the Investigational Medicinal Product Dossier (IMPD).

The product is manufactured and supplied to the clinical sites in monodose vials. One vial, for one administration, contains 3.7 GBq (100 mCi) or 7.4 GBq (200 mCi) of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at calibration time (the time of infusion). The variability of the volume depends on the time between the calibration date and the production date. The product will be shipped and calibrated for use at 24h or 48h after production in a centralized GMP facility. The calibration time of a dose depends on the distance from the manufacturing facility to the clinical sites. The amount

of administered radioactivity is specified at the time of infusion. Additional information on recommendations for treated patients are provided in Appendix F.

Chemical-physical properties of each dose are listed in the Table 10.

Table 9. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Infusion Solution Composition.

Component	**Composition (one vial)**	**Function**
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	7.4 GBq / 200 mCi	Active Pharmaceutical Ingredient
X-DOTA^{0}-Tyr^{3}-Octreotate	[redacted] µg/mL	Total peptide content
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	[redacted] µg/mL*	Active Pharmaceutical Ingredient
DOTA^{0}-Tyr^{3}-Octreotate	[redacted] µg/mL*	Active Pharmaceutical Ingredient Precursor
Volume	From 22-25 mL	
Specific Activity (GBq/Total peptide)	[redacted] GBq/µmol (at EOP)*	
Radioconcentration	370 MBq/mL (at EOP)	
Other Constituents/Excipients	mg/mL	
[redacted]	[redacted]	pH adjuster
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Radiation Stability Enhancer
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Masking Agent
[redacted]	[redacted]	Blood isotonic solution
Water for Injection	-	Solvent

*Values calculated assuming ^{177}Lu specific activity of 740 GBq/mg at labelling time and a mean synthesis yield of [redacted] and radiochemical purity [redacted]

Treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will consist of a cumulative dose of 14.8 GBq (400 mCi) or 29.6 GBq (800mCi) with the dosing equally divided among 4 administrations of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate at 8±1-weeks intervals.

9.1.2 Handling

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate must be administered at the investigational site. The study medication must be stored, handled and administered only by qualified/authorized personnel and must be prepared in accordance with pharmaceutical quality requirements, and radiation safety regulations for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate.

9.1.3 Packing and Labeling

^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will be prepared, packaged, labelled, and released under the responsibility of Advanced Accelerated Application´s Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations. Instructions for shipment, storage and handling of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate Solution of Infusion are provided in Appendix G.

9.1.4 Destruction

The used/unused medications, except for ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, which will be locally discarded, will be returned to the proper local depot for destruction at the study completion or upon expiration, according to IPM/Sponsor decision and approval.

9.2 Nivolumab

9.2.1 Description

Product name	Nivolumab Injection, 100 mg/vial (10 mg/mL)
Product description and Packaging	Packaging: Vials assembled into dispensing boxes containing 5 vials of 100 mg Nivolumab Vials: 10 cc Type I glass vial, 20 mm stopper and seal Appearance: Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.
Product Ingredients	Each vial contains Nivolumab 100 mg active

9.2.2 Handling and Dose preparation

As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab infusions should be prepared in a laminar flow hood, glovebox, or safety cabinet using standard procedures for the safe handling of intravenous agents applying aseptic techniques. Gloves are required. If nivolumab solution comes in contact with the skin or mucosa, immediately and thoroughly wash with soap and water.

9.2.3 Dose Preparation and administration

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Preparation

- Withdraw the required volume of nivolumab and transfer into an intravenous container.

- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. For dilution, nivolumab injection may either be added to an empty infusion container and then further diluted by addition of NS or D5W, or the nivolumab injection may be added directly to an appropriate volume of NS or D5W in a pre-filled infusion container.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab according to protocol section 9.2.4.

Storage of Infusion

The product does not contain a preservative. After preparation, store the nivolumab infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion

OR

- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
  Do not freeze.

9.2.4 Study Drug Destruction

Study drugs (those supplied by BMS or sourced by the site/investigator) can to be destroyed on site if local policies allow to do so. It is the Investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed following BMS approval and after being inspected and reconciled by the responsible site manager (SMN). If required by local country/hospital regulations drug can be returned to an off-site drug destruction vendor, but should only be completed with your SMN while they are on site. All drug destruction whether performed on or off site should be documented using the Investigational Product Return Form or local form as provided by SMN.

10.0 CORRELATIVES/SPECIAL STUDIES

Contribution to correlative studies by each site is recommended and encouraged by the Sponsor, but is optional for the participating sites.

10.1 Pathology correlative studies

PD-L1 protein expression in pretreatment tumor biopsy samples will be evaluated using a validated automated immunohistochemistry (IHC) assay (Dako, Carpinteria, CA, USA) that uses a rabbit monoclonal PD-L1 antibody (clone 28-8; Epitomics Inc, Burlingame, CA, USA). We will assess whether PD-L1 expression is associated with the clinical outcome following administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab. PD-L1 expression will be categorized as positive

if ≥ 1% of tumor cells in a section that includes ≥100 evaluable tumor cells display PD-L1. Different cut-off values will also be assessed retrospectively.

Acknowledging the difficulties in obtaining fresh tumor samples in SCLC, utilization of archival tumor material will be allowed. Optional tumor biopsies from consenting patients will also be performed at the following times.

- Prior to treatment
- At the time of progression

If sufficient material is available, in addition to PD-L1, other biomarkers in the tumor and stromal compartments including SSTR2, TIM-3, VISTA, FOXP3, LAG3, and IDO-1 may be analyzed. Expression of downstream signaling molecules of SSTR2 (e.g. AKT, MYC) may also be investigated.

Each patient sample set will be assigned a unique patient identifier. The protocol scientific investigator(s) handling the samples will be blinded as to the patient identification, patient data and outcome.

10.2 Specimen Banking

Patient samples collected at Georgetown University and sent from an outside institution will be retained in the Dr. Giaccone's lab.

Giuseppe Giaccone, M.D., Ph.D.

Research Building, Room W503

Georgetown University

3970 Reservoir Road NW Washington DC 20007

Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Dr. G. Giaccone will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Georgetown University Medical Center. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a phase I/II clinical trial of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab, in patients with ES-SCLC. The primary endpoint of the phase I portion is to determine the recommended phase II doses of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate when given in combination with nivolumab. Patients with relapsed or refractory ES-SCLC and patients with advanced or inoperable grade I-II pulmonary NETs are also eligible for the phase I portion. For all patients participating in this phase I/II study, a positive SRI (Somatostatin Receptor Imaging) scan showing overexpression of SSTR2 will be mandatory for inclusion (NETSPOT®). The phase II portion will consist of patients with ES-SCLC that completed standard first-line chemotherapy with a platinum-based regimen, without disease progression (responders plus stable disease) at the time of initiation the combination therapy with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab. Patients will be randomly allocated in two arms: one will be treated with the combination of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab, and the other arm will continue be followed (observation) after completion the standard chemotherapy treatment. Cross-over will be permitted at the time of disease progression.

11.2 Sample Size and Accrual

ES-SCLC (i.e. SCLC that has spread beyond the supraclavicular areas or with distant metastases) remains incurable with current management options, and patients are treated with combination chemotherapy. Several chemotherapy combinations are active in SCLC, but usually a platinum-containing regimen is chosen. The ORR of platinum-based therapy administered to patients with ES-SCLC ranges from 40 to 80%, and the median PFS ranges from 5 to 7 months in patient series treated in a clinical trial setting (phase-II/III studies) [9, 10, 48-55]. A placebo-controlled randomized phase II study of maintenance sunitinib shows that median PFS was 2.1 months in the placebo group[56].

Based on historic average clinical outcomes, we propose a clinical study that will be integrated by a dose finding approach followed by a randomized phase II study with PFS as the primary endpoint, designed to have 80% power for a two-sided 0.05 level test. The completion of the first part of the study will require approximately 8-9 months for accrual assuming 9 to 12 patients will be required for the completion of the phase I portion with the participation of 7 institutions (Georgetown Lombardi comprehensive Cancer Center, Memorial Sloan Kettering Cancer Center, University of California, Los Angeles, University of California, San Francisco, Vanderbilt University, Hackensack University Medical Center, and Walter Reed National Military Medical Center).

For the phase II portion, assuming a median PFS of 2 months following completion of first-line therapy with a platinum-based chemotherapy for ES-SCLC in the control arm, and an expected median PFS of 5 months for the maintenance therapy with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate and nivolumab in the experimental arm (hazard ratio 0.4), it will be required to document 40 PFS events from a total population of 44 patients enrolled during a period of 18 month, including a minimum follow up of 10 months, with an expected accrual rate of 3-4 patients per month and the participation of 6-7 institutions. Assuming a potential 15% dropout, the total number of patients to recruit will be 52 [57-59].

After the dose finding of the phase 1 portion is concluded, the phase 2 will start. The major end of the phase I is the safety and tolerability. Activity will not be adequately assessed in the phase I portion. The total number of patients required for the whole study will be 61-64 (phase I: 9-12 patients, phase II: 52 patients).

11.3 Data Analyses Plans

PFS will be defined as the time from random assignment to disease progression or death from any cause, whichever comes first. OS will be defined as the time from random assignment to death from any cause; living patients will be censored at the date of last follow-up. Survival will be estimated and plotted by the Kaplan–Meier method. In addition, the median progression-free and overall survival times will be reported along with the 95% confidence intervals. The cox proportional hazards regression model will be used to obtain hazard ratios (HRs) and the log-rank test will be utilized to compare survival estimates between the maintenance group and the control observation group. Secondary endpoints will be analyzed when the required number of events for the primary endpoint (PFS) has been met. The DCR is defined as the proportion of patients with a best overall response of CR, PR, or SD. The ORR is defined as the proportion of patients with a best overall response of CR or PR. All randomized subjects will consist of the safety population. This population will be used for all summaries of safety data (AEs, concomitant medications, laboratory data). P-values less than 0.05 will be considered significant. All statistical analyses will be performed using SAS (Version 9.4; SAS Institute, Cary, NC). Dr. Ming T. Tan will serve as the study statistician.

12.0 STUDY MANAGEMENT

12.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

12.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Research office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

12.3 Registration Procedures

The study site coordinator or physician is responsible to screen potential subjects using the eligibility criteria, obtain informed consent and HIPAA authorization forms from each consenting subject, and to provide the Eligibility Packet (defined below) to the Quality Assurance Office (QAO) for review. The QAO is responsible to verify eligibility of all subjects screened to investigator initiated or multi-site clinical research trials, to assign subject IDs to each eligible patient, and to inform the study site of the assigned subject ID or any eligibility issues within one business day.

Subjects may not begin treatment until eligibility is confirmed and subject ID is assigned by QAO.

Procedures:

1. Patient signs Informed Consent Form (ICF) and HIPAA authorization form.
    - ICF is administered by site coordinator or treating physician.
2. Site screens subject for eligibility criteria
    - Site coordinator or treating physician completes eligibility checklist
    - If patient does not meet eligibility criteria, stop and report screen failure.
3. Site faxes the eligibility packet to QAO at 202-687-9361 or emails the packet to LCCCQAO@georgetown.edu
    - Eligibility Packet to include:
        - Completed QAO Registration Form
        - Signed and dated Eligibility Checklist, completely filled out
        - Signed and dated ICF
        - Signed and dated HIPAA authorization form
        - All source documents required for verification of eligibility
4. QAO verifies eligibility using Eligibility Packet

- If eligibility is not verified, stop and inform site of eligibility issues or questions

5. If eligibility is verified, QAO does the following:
   - Assigns Subject ID
   - Registers the patient in the study and in the CTMS
   - Emails the Subject ID to the study site within one business day of receiving the Eligibility Packet

12.4 Data Management and Monitoring/Auditing

The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this trial. As this study is an investigator initiated Phase I/II study it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Study Chairs and Associate Investigators will review the data including safety monitoring at their monthly teleconferences of participating sites.

All "reportable" (defined above) Severe Adverse Events (SAEs) are required to be reported to the local and to the Georgetown IRB, as detailed above, and to the chair of the DSMC. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every three months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the Study Chair to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial Study Chair and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the Study Chair must act to implement the change as expeditiously as possible. In the unlikely event that the Study Chair does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The Study Chair, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at GU-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

Of note, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. The multi-institutional coordinator will be tasked with the job of collecting all primary source documentation for patients enrolled outside of Georgetown University. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review. Faxed records should be sent to Gabriela Gomez with an email to the multi-institutional coordinator and Dr. Giaccone to confirm receipt of those records.

12.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

12.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

12.5.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

12.5.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

12.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix A. GUIDANCE ON CONTRACEPTION

ACCEPTABLE METHODS FOR PROTOCOLS WITH A TERATOGENIC DRUG OR WHEN THERE IS INSUFFICIENT INFORMATION TO DETERMINE TERATOGENICITY

(CHOOSE ONE OF THE FOLLOWING 3 OPTIONS)[a]

- OPTION 1: Any TWO of the following methods
  - Hormonal methods of contraception[b, c, d]
  - IUD[c, d, e]
  - Vasectomy[d, f]
  - Tubal Ligation[d]
  - A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide, Diaphragm with spermicide)
- OPTION 2: Male condom (with spermicide) and diaphragm[g]
- OPTION 3: Male condom (with spermicide) and cervical cap[g]

[a] The theoretical failure rate for any of the options listed is considerably less than 1% per year

[b] Excludes progestin-only pills

[c] Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected by the investigational drug in the protocol or there is compelling evidence to substantiate that investigational product(s) or con-meds will not adversely affect contraception effectiveness. The use of hormone based contraceptives is not otherwise restricted.

[d] A highly effective method of birth control with a failure rate less than 1% per year.

[e] IUDS used should have a failure rate less than 1% (highly effective method), such as Mirena and ParaGard.

[f] Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia.

[g] These 2 barrier methods together are acceptable for a teratogenic drug.

UNACCEPTABLE METHODS OF CONTRACEPTION

- No method
- Withdrawal
- Rhythm
- Vaginal Sponge
- Any barrier method without spermicide
- Spermicide
- Progestin only pills
- Concomitant use of female and male condom

Appendix B. Immune-related toxicity management algorithms.

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

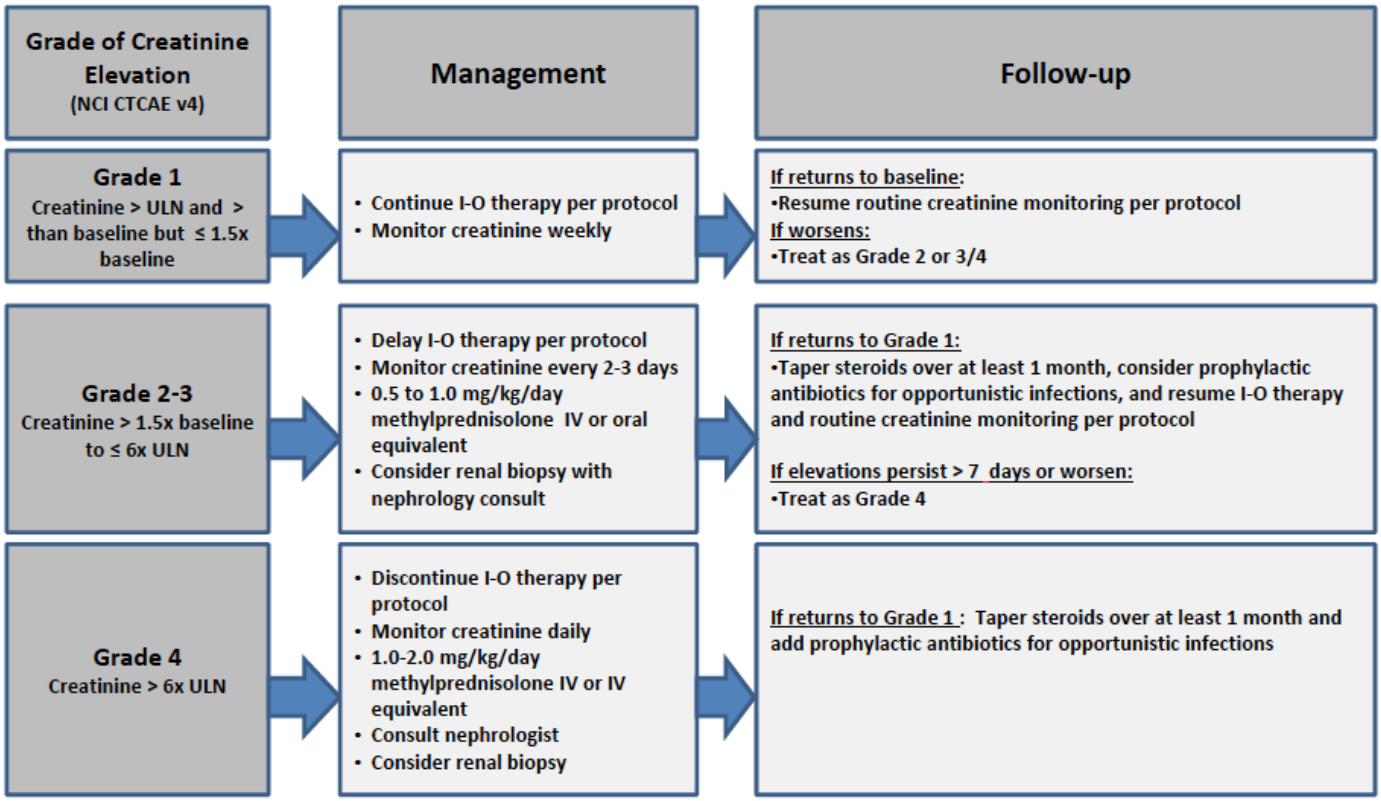
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

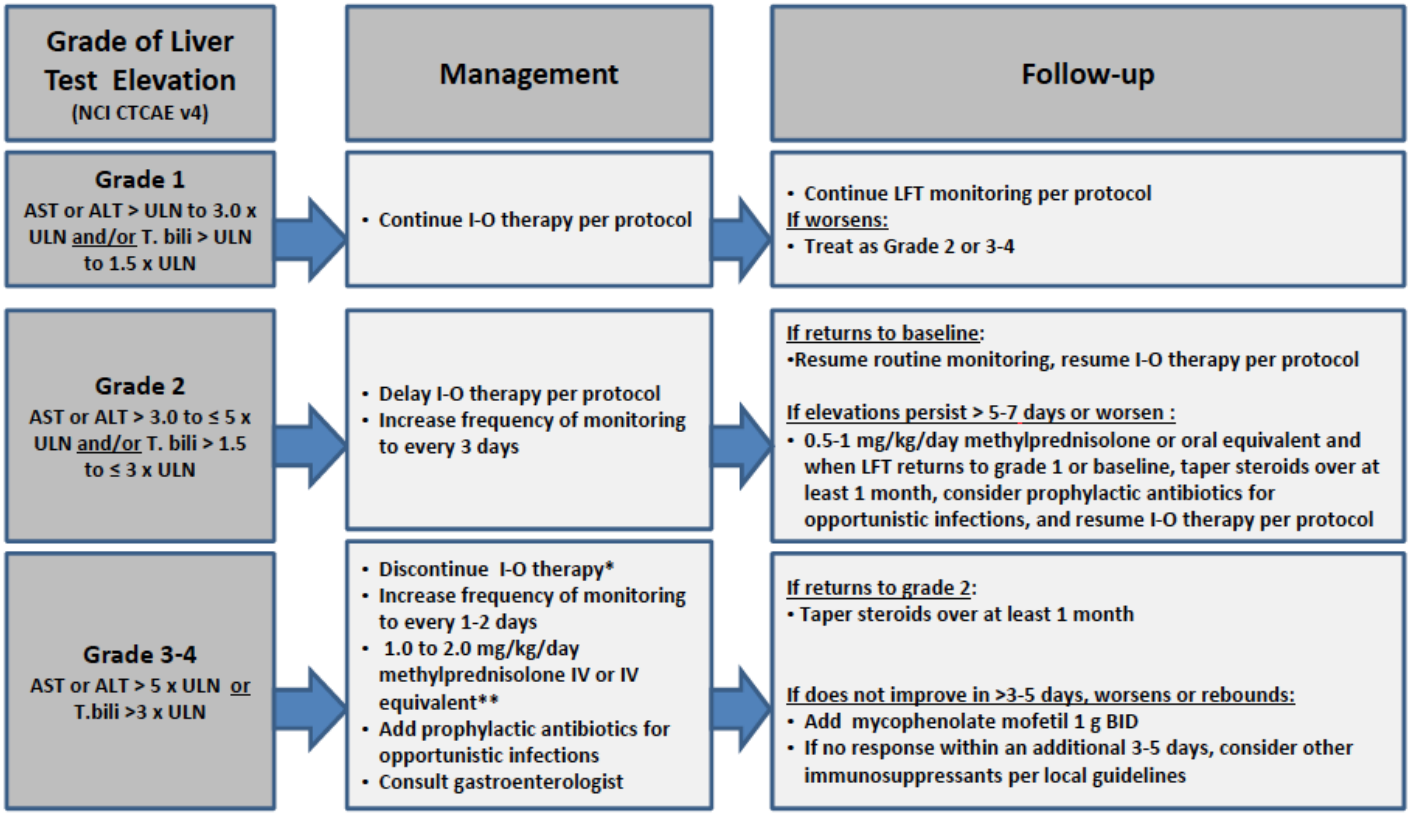
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



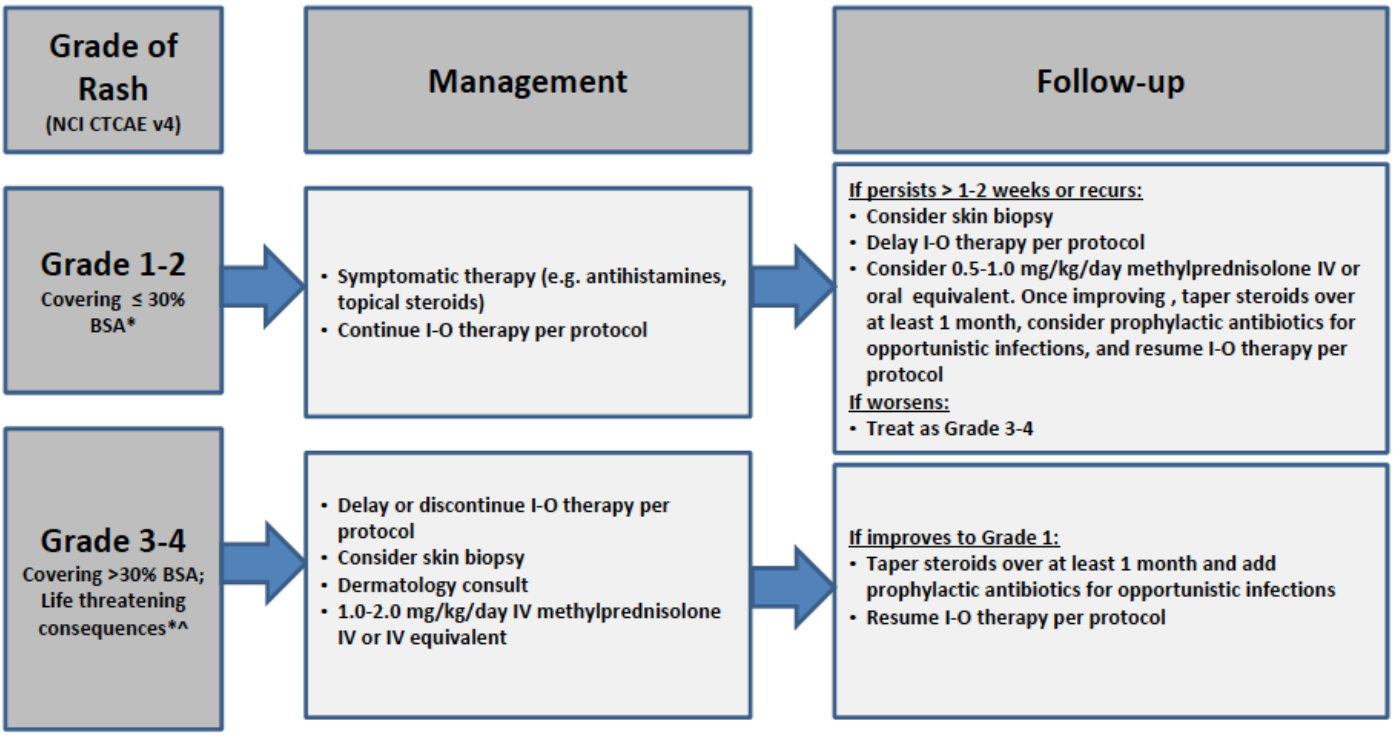
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Skin Adverse Event Management Algorithm

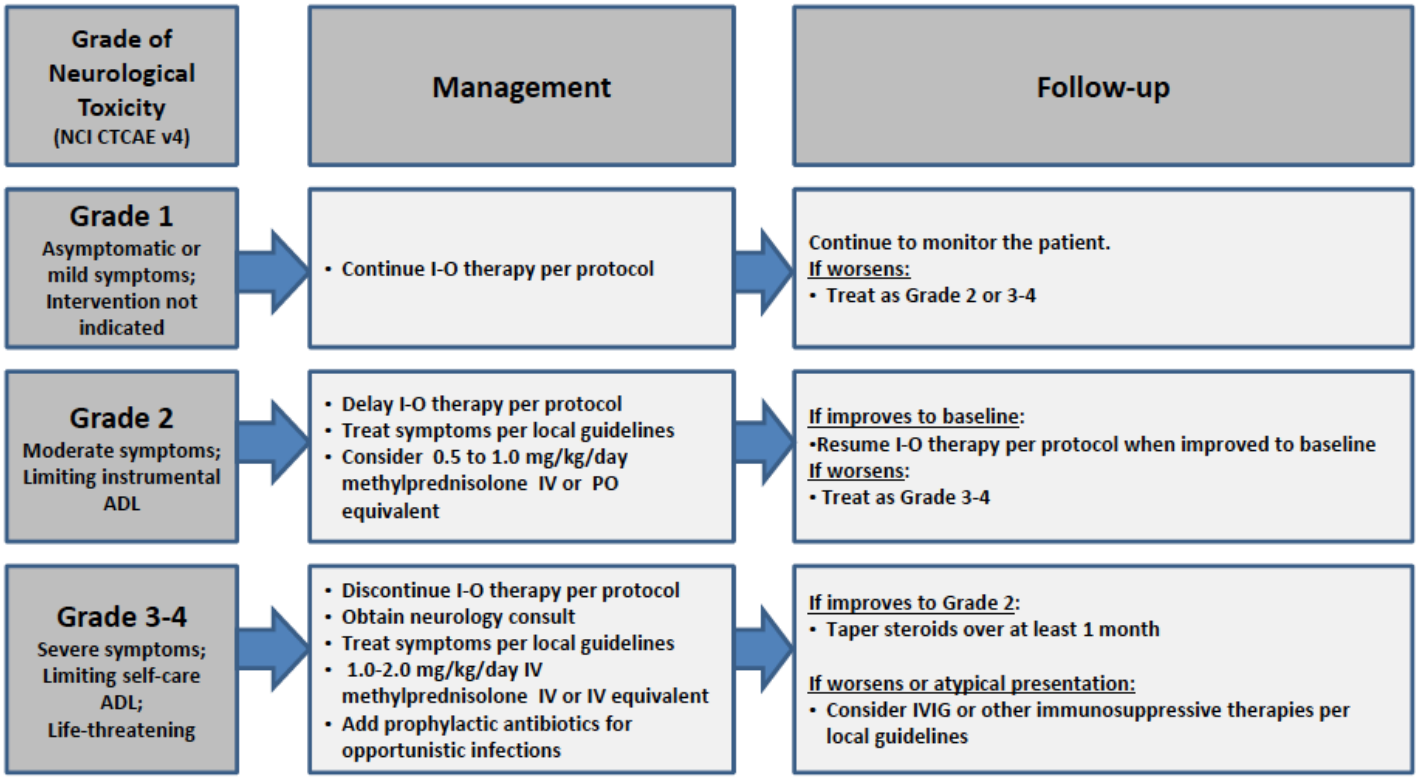
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

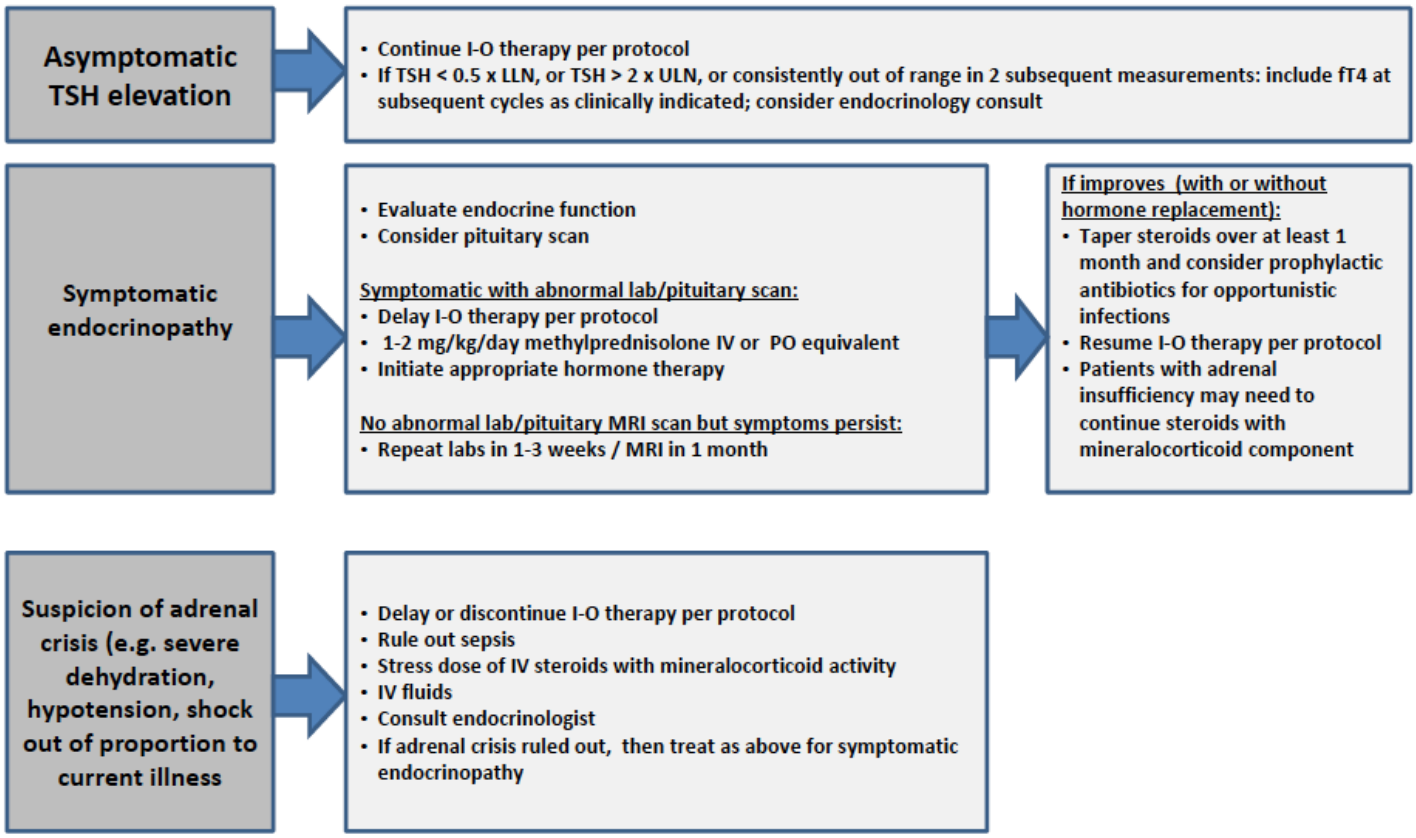
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Appendix C. ECOG Performance Status Score

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

ASSESSMENT/EVENT	Screening	Treatment Period*									
Study Visit		C1	C1	C1	C1	C2 and beyond	C2 and beyond	C2 and beyond	C2 and beyond	EOT	Follow-up
		D1	D15	D29	D43	D1	D15	D29	D43		
Informed consent	X										
ECOG PS	X	X	X	X	X	X	X	X	X	X	
History and physical examination	X	X	X	X	X	X	X	X	X	X	
Adverse event assessments		X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	
Height and weight	X										
Concomitant Medications Collection	X	X	X	X	X	X	X	X	X	X	
12 Lead ECG	X										
Tumor imaging[a]	X					X					
Brain imaging (MRI or CT)	X	To be performed as clinically indicated at the discretion of the investigator									
FDG-PET	X	To be performed as clinically indicated at the discretion of the investigator									
NETSPOT PET[b]	X					X[c]					
CBC with differential	X	X[j]	X	X	X	X	X	X	X	X	
PT/aPTT	X										
Comprehensive Metabolic Panel	X	X[j]	X	X	X	X	X	X	X	X	
Thyroid function test[d]	X			X		X		X		X	
LDH	X	X[j]	X	X	X	X	X	X	X	X	
Magnesium	X	X[j]	X	X	X	X	X	X	X	X	
Phosphorus	X	X[j]	X	X	X	X	X	X	X	X	
Amylase	X										
Lipase	X										
HBsAg[e]	X										
anti-HCV[e]	X										
anti-HIV[e]	X										
Pregnancy test[f]	X		X[f]				X[f]				
Tumor biopsy	X[g]	Optional at the time of progression									
Nivolumab[h]		X	X	X	X	X	X	X	X		
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate			X				X[h]				
Long-term follow up including survival											X[l]

a: Initial tumor assessment will be performed at C2 D1 (± 7 days) and every 8 weeks (± 7 days) thereafter.
b: Refer to section 6.1 for details
c: On treatment Netspot only on cycle 2 day 1 (± 3 days)
d: Thyroid function testing will be done every cycle on day 1 (± 3 days) and day 29 (± 3 days). Does not need to repeat on C1D1.
e: Within three months prior to starting study treatment
f: Only for women of child bearing potential (WOCBP). Within 24 hours prior to the administration of ^{177}Lu-DOTA0-Tyr3-Octreotate.
g: Optional. Utilization of archival tissue will be allowed.
h: May be given one day earlier or delayed up to 1 week. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate will only be given for 4 cycles.
i: Annually for two years
j: C1D1 laboratory tests do not need to be repeated if the screening laboratory tests were done within 7 days from C1D1.
* Refer to section 6.2 for details about time windows within which each procedure should be performed.

Appendix D. Study Calendar

Appendix E. Mandatory Adverse Event Reporting Information for Nivolumab

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
- Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the

sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
- 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 should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.
- SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

SAEs should be reported on MedWatch Form 3500A, which can be accessed at:
http://www.accessdata.fda.gov/scripts/medwatch/

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH

5600 Fishers Lane

Rockville, MD 20852-9787

Fax: 1-800-FDA-0178 (1-800-332-0178)

http://www.accessdata.fda.gov/scripts/medwatch/

A **nonserious adverse event** is an AE not classified as serious.

Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. 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.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such. The following laboratory abnormalities should be documented and reported appropriately:

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

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g. dose tapering if necessary for subject safety). The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures. 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 Surveillance Form

[provided upon request from BMS]. Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

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.

Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Appendix F. Recommended Precautions for Patients Treated with ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera)

In accordance with the medical staff, you have agreed to receive a treatment using a radioactive medicine. We think that the potential activity of this medicine in treating your tumor is due to the radioactivity of this medicine; it is also for this reason that it is necessary to follow certain precautions in order to limit the exposure of the people around you and to avoid contaminating them with radioactivity.

Because of knowledge and experience in the field, it is estimated that the health risks to your family members and the general public are low because of the physical and radiopharmaceutical properties and the metabolism of the radiopharmaceutical. You must adhere to the following rules to maximize the safety of other persons. They are the result of many years of experience in the use of radioactivity in medicine, and they include recommendations by international organizations.

1. General rule

You must avoid close contact with people who live with you, and should try to keep a distance of at least one meter for 7-days after you receive Lutathera.

2. Use of toilets

Toilets must be used in a seated position, even for men. It is absolutely necessary to use toilet paper each time. It is equally important to wash your hands to avoid contaminating the door handles. It is strongly recommended to move your bowels every day and use a laxative if you need help. Furthermore, empty your bladder (urinate) frequently, every hour for example, on the day you received treatment and for two days after. Follow your doctor’s advice on how much fluid to drink. After expelling fluids, drink a glass of water. You can substitute juice or a sports drink as a means to replace expelled fluids. Follow any additional advice that your doctor provides on how much to drink.

3. Contact with children (less than 10 years old)

Because of the high sensitivity of children to radioactivity, it is strongly advised to limit contact to them to less than 15 minutes for each day while keeping a distance of at least 1-2 meters. It is strongly recommended that there be no contact with children who are less than 10 years old for 7-days after the administration of Lutathera.

4. The spouse and people in the family circle

It is strongly advised to sleep in separate beds at a distance of at least 1 meter. Embraces and sexual activity are not advised for eight days after the administration of Lutathera.

5. Seniors

Older people are less sensitive to radioactivity (between 3 and 10 times less than a middle-aged person). Therefore, the previous recommendations can be followed with a little more flexibility in the presence of the elderly.

6. Contact with pregnant women

Contact with pregnant women should follow the same restrictions recommended for children less than 10 years old.

7. Breastfeeding

Breastfeeding should be stopped because it is not compatible with a treatment using a radioactive product.

8. Pregnancy

Pregnancy must be excluded before the start of treatment. Any woman who has missed a period must be assumed to be pregnant until proven otherwise and alternative therapies which do not involve ionizing radiation must be then considered.

There is a potential risk that ionizing radiation by Lutathera could cause toxic effects on female and male gonads. Due to the nature of the compound, women of child-bearing potential, as well as males, must abstain from procreation (using effective contraceptive measures) during and up to 6 months after treatment with Lutathera.

9. People who need extra assistance

People who are confined to the bed or have reduced mobility will preferably receive assistance by a care provider. It is recommended that when providing assistance in the bathroom, the care provider wear disposable gloves for 2-3 days after administration. In the case of the use of special medical equipment such as catheters, colostomy bags bedpan, water nozzle, or anything that could be contaminated by your body fluids they must be emptied immediately in the toilet and then cleaned. If anyone helps you clean up vomit, blood, urine, or stool they should wear plastic gloves; the gloves should then be put in the specified trash plastic bag.

10. Dishes and bathroom accessories

For the first two days after your treatment wipes and/or toilet paper must be flushed down the toilet. Always wash your hands well after using the toilet. It is strongly recommended to shower

every day for at least the first 7 days after your treatment. Try to flush any tissues or any other items that contain anything from your body, such as blood, urine and faeces down the toilet (at least for two days after the therapy). Items that cannot be flushed, such as menstrual pads and bandages, must be placed in specified plastic trash bags.

Wash your underwear, pajamas, sheets and any clothes that contain sweat, blood or urine separately from the laundry of others in your household. Wash your items two or three times; use a standard washing machine; you do not need to use bleach and do not need extra rinses.

11. Trash recommendations

Keep the specified plastic trash bags separate from other trash; keep the bags away from children and animals. A member of the Study Staff will tell you how and when to get rid of the specified plastic trash bag; you may be asked to bring the bag back to your treatment facility, or, after 70 days, the bag may be removed as other trash bags.

12. Professional activities

Lutathera could affect your ability to drive and to use machines, as dizziness has been reported as a common side effect. If there is a risk of frequent contact and being in close vicinity to the public and/or with children, the activity must be temporarily suspended.

13. Use of public transportation

For short trips (less than 30 minutes), the precautions are minimum. If you ride with someone else, confirm she is not pregnant, and maintain a distance of >1 meter (use the back seat on opposite side of the driver). If you are able to do so, it is best to drive yourself.

14. Public activities

Avoid assisting in shows or public meetings which could expose third-parties for more than 30 minutes in the first week after your treatment.

Ask Your Doctor or a member of the Study Staff when:

- It will be safe to eat out, go shopping and attend events such as religious services, parties and movies;

- You will be able to return to work and to care for or teach others;

- It would be safe to donate blood;

- Special or longer distance travel is possible (Note: For up to 3 months or more following radioactive treatment you may set off radiation detectors at: national borders, airports, bus and

train stations, tunnels, bridges, trash collection sites and even your place of employment); a member of your Study Staff will issue you a letter or card describing the therapy and the phone number of a person knowledgeable about your treatment (usually at the treating facility) in case local law enforcement agents need to check on this information; you should keep the letter or card containing the information with you whenever you are travelling for at least 3 months.

15. Hospitalization

In the case that an unplanned hospitalization occurs, it is important to notify your doctor. There is a possibility that due to an excessive release of hormones following the administration of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate your doctor may request that you stay in hospital overnight for observation and treatment if necessary, normally consists of intravenous fluids, corticosteroids and the correction of any chemical imbalance in the blood.

16. Domesticated animals

The lifespan of domesticated animals is much less than that of humans. Therefore, the effect of the radioactivity is less. It is not necessary to take any particular precautions. But do not sleep with pets (ask your doctor for how long) since your secretions may be carried away by the pet.

17. Emergency Care

You will get an information card or letter at the time of your treatment that will show the date, type and amount of radioactivity that you were treated with; carry this card with you at all times for at least 3 months following your treatment.

If you are in a traffic accident or any other medical emergency and require medical assistance during the first week after your treatment, you should show this card to the medical providers to let them know about the date and dose of your radioactive treatment.

18. Important information for patients on risks of radiation

Radiation exposure to others should always be As Low As Reasonably Achievable, a goal often abbreviated as ALARA. If you follow the above advice, the radiation from you to others is likely to be less than what they receive from radiation in nature over a year's time.

Please phone us if:

- you have any questions, and particularly if
- any of the above instructions cannot be followed and/or if
- you see anything that may have accidentally or unavoidably increased exposure of others to

- radiation.

19. Recommended Precautions after Lutathera treatments

		mCi (MBq) administered			
		200 (7400)	200 (7400)	200 (7400)	200 (7400)
		Precaution Days			
Night-time restrictions					
	Sleep in a separate (1 meter separation) bed from adults for days shown	8	8	8	8
	Sleep in a separate bedroom from pregnant partners, infants, or children for days shown	15	15	15	15
Day-time restrictions					
	You may return to work after days shown	8	8	8	8
	Maximize your distance (1 meter) from children and pregnant women for days shown.	8	8	8	8
	Avoid extended time in public places for days shown	8	8	8	8

Appendix G. Instructions for Shipment, Storage and Handling of 177Lu-DOTA0-Tyr3-Octreotate (Lutathera) Solution for Infusion

Name of the medicinal product

Lutathera 7400 MBq, radiopharmaceutical solution for infusion

Qualitative and quantitative composition

Lutathera is supplied as a ready for use radiopharmaceutical solution for infusion.

A vial contains 7400 MBq of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate with a specific activity greater than 53 GBq/umol and with a radioconcentration of 370 MBq/mL at end of production.

Pharmaceutical form

Sterile Solution for infusion.

Clear, colorless or slightly yellow solution.

Pharmaceutical components

List of excipients

[redacted]

Water for Injection

Shelf life

72 hours after end of production.

Special precautions for storage

Store below 25°C.

Store in the original package for radioprotection purposes.

The product must be stored according to national regulations concerning radioactive products.

Nature and contents of container

A 30 mL vial, colorless Type I glass, closed by a rubber stopper and sealed by an aluminum cap. One vial contains 22 to 25 mL of solution. The vial is inserted into a lead shielded container protected by a plastic sealed container closed in a Type A package (according to the Accord Dangereuses Route agreement or ADR).


Type A container


Plastic container