



BROWN
Oncology Research Group

BrUOG 379: A Phase Ib/II Single Arm Study of ONC201 plus Nivolumab in Microsatellite Stable (MSS) metastatic colorectal cancer (mCRC) patients

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PROTOCOL SYNOPSIS

Title: **BrUOG 379:** Phase Ib/II investigator-initiated, single arm study of ONC201 plus Nivolumab in microsatellite stable (MSS) metastatic colorectal cancer (mCRC) patients

Drugs: ONC201 (Oncoceutics)
Nivolumab; Opdivo (BMS)

Phase: Ib/II

Rationale for combination of ONC201 with anti-PD1 Opdivo (Nivolumab):

The combination of ONC201 with anti-PD-1 therapy resulted in more potent *in vivo* tumor suppression with the combination versus anti-PD-1 therapy alone

Hypothesis: We hypothesize that ONC201 is a novel mCRC therapy that acts through TRAIL innate immune and cell mediated NK, and T cell signaling to inhibit tumor growth and metastases, and that anti-tumor effects (disease control, prolonged PFS > 2 mo) will be observed in patients who receive ONC201 in combination with Nivolumab.

Objectives:

Primary:

Phase Ib: Primary Objective

- 1) Determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of ONC201 when administered orally in combination with Opdivo (Nivolumab) in patients with microsatellite stable metastatic colon cancer who progressed after at least 2 lines of therapy

Phase Ib: Secondary Objectives

- 1) Evaluate the overall safety profile of orally-administered ONC201 in combination with Opdivo (Nivolumab) using CTCAE version 5.0
- 2) Evaluate the pharmacokinetic (PK) profile of orally-administered agent ONC201 in combination with Opdivo (Nivolumab)

- 3) Assess the pharmacodynamic effects of orally-administered agent ONC201
- 4) Assess the efficacy of ONC201 and nivolumab.

Phase II:

Primary Objective:

- 1) Determine progression free survival (PFS) of orally-administered ONC201 in combination with Opdivo (Nivolumab)
- 2) Determine the response rate to ONC201 in combination with Opdivo (Nivolumab), as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1, in patients with microsatellite stable metastatic colorectal cancer

Secondary Objectives:

- 1) Confirm safety of phase II dose of ONC201 in combination with Opdivo (Nivolumab) using CTCAE version 5.0
- 2) Assess preliminary overall survival associated with ONC201 and Opdivo (Nivolumab) in patients with microsatellite stable metastatic colorectal cancer
- 3) Correlate clinical outcome with tumor & blood biomarkers including cancer stem cells, signaling intermediates and inhibitors, NK cells, TRAIL, granzyme, perforin, and M30.

Study Period:

The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months, as determined by the investigator. The study is expected to be completed over an approximate 3.5-year period

Study Design:

This is a single arm Phase Ib/II, open label, safety, pharmacokinetic (PK), pharmacodynamics (PD) and efficacy study of ONC201 in combination with Opdivo (Nivolumab) in adult patients with metastatic colorectal cancer who progressed after at least 2 lines of chemotherapy.

This is a phase Ib/II study that will enroll patients with microsatellite stable (MSS) metastatic colorectal cancer (mCRC)

Phase Ib Dose Level ONC201 (625 mg PO weekly) plus Nivolumab (240 mg IV Q2 weeks).

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Phase II Stage at Recommended Phase II Dose (RP2D).

Planned Enrollment

Phase Ib: Approximately 6 patients

Phase II: A total of 34 patients will be treated at the RP2D (including 6 patients from the Phase IB treated at the RP2D and 28 patients from phase II). Interim safety analysis after 12 patients accrued at the RP2D, interim efficacy analysis after 17 patients.)

Eligibility Criteria:

Inclusion: Patients aged \geq 18 years must have a histologically/cytologically -confirmed primary MSS colorectal tumors who progressed after at least 2 lines of treatment

Exclusion: Patients with symptomatic brain metastases. Patients with inflammatory and autoimmune diseases or other medical disease in which Nivolumab is contraindicated. Patients with prior ONC201 will be excluded.

Randomization:

This is a single arm study with no randomization. All enrolled patients will receive the study drugs.

Correlative Studies

Pre- and post-treatment biopsies are mandatory to evaluate tumor infiltration of NK, T cells, cancer stem cells. Tumor biopsies will be used to evaluate integrated stress response (ISR), TNF-related apoptosis-inducing ligand (TRAIL), DR5, granzyme, perforin, cell death, cell proliferation. PD-1 and PD-L1 testing will all be performed.

1 INTRODUCTION

The Phase I portion of the study will determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ONC201, when given in combination with Nivolumab to patients with microsatellite stable (MSS) advanced metastatic colorectal cancer (mCRC) who progressed on at least two lines of therapy. Identification of the MTD and/or RP2D will assist in the design of the Phase II portion. The Phase II study will assess efficacy and refine safety assessments of the drug combination.

2 Study population

This trial will enroll adult patients with advanced mCRC who progressed after at least 2 lines of therapy. ONC201 is an investigational agent. Nivolumab (Opdivo) has been approved in patients with microsatellite instability-high (MSI-H) or mismatch repair (MMR)-deficient mCRC.

2.1 Background

2.1.1 Opdivo (nivolumab) Anti-PD1

In the tumor microenvironment, program death -1(PD-1) and its ligand PD-L1 and PDL-2 perform a vital role in tumor progression and survival by escaping tumor neutralizing immune surveillance. Binding of the PD-1 ligands, to the PD-1 receptor inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands in cancer contributes to inhibition of active T-cell immune surveillance.

Opdivo (nivolumab) is a humanized monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth in several malignancies.

In the recent years, FDA granted approval of Nivolumab as a single agent or in combination in several malignancies: including treatment (as a single agent or in combination with ipilimumab) of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) in adults and pediatric patients, treatment of recurrent or metastatic squamous cell carcinoma of the head and neck in patients with disease progression on or after platinum-based therapy, treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib, treatment of classical Hodgkin lymphoma (cHL) in adult patients that have relapsed or progressed following autologous hematopoietic stem cell transplant (HSCT) and brentuximab vedotin, or after 3 or more lines of systemic therapy that included autologous HSCT, adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease following complete resection, treatment (as a single agent) of unresectable or metastatic melanoma, treatment of metastatic non-small cell lung cancer (NSCLC) that has progressed on or after platinum-based chemotherapy, treatment (as a single agent) of advanced renal cell cancer (RCC) in patients who have received prior anti-angiogenic therapy, treatment of intermediate or poor risk, previously untreated advanced RCC (in combination with ipilimumab), Treatment of metastatic small cell lung cancer (SCLC) in patients with progression after platinum-based chemotherapy and at least one other line of therapy, treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression during or following a platinum-containing therapy

2.1.2 ONC201

ONC201 (TIC10) is a first-in-class small molecule that activates the integrated stress response (ISR) in tumor cells that leads to downstream anticancer effects that include inactivation of pro-

survival Akt and ERK signaling along with induction of the TRAIL pathway (Allen et al., 2013). The efficacy of ONC201 has been consistently demonstrated in numerous *in vitro* and *in vivo* experiments (subcutaneous, orthotopic, and transgenic) by multiple institutions. Despite its strong cytotoxicity in tumor cells, ONC201 does not induce cell death in normal cells. *In vivo* studies indicate that the safety margin (ratio of therapeutic dose to lowest dose with a mild adverse event) of ONC201 is at least 10-fold in rats and dogs in GLP toxicology studies. The profile of ONC201 is well suited for an oncology product: preclinical efficacy with infrequent administration, broad-spectrum activity independent of mutations or disease type, orally active, compelling safety profile, combines synergistically and safely with many approved therapies, highly active by employing a combination of established anti-tumor/pro-apoptotic pathways, highly stable, water soluble, and can penetrate the blood-brain barrier. In summary, preclinical studies suggest that ONC201 is an orally active antitumor agent with a remarkably benign safety profile given its broad-spectrum activity demonstrated in a variety of aggressive cancer models.

2.1.2.1 Preclinical Efficacy

ONC201 induces broad-spectrum cell death in tumor cells harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that render resistance to chemotherapies and targeted agents. ONC201 induces caspase-mediated apoptosis in cancer cell lines and exhibits broad-spectrum cytotoxicity *in vitro*. ONC201 has demonstrated single agent anti-tumor effects in several solid tumor models (Figure 1) that include subcutaneous and orthotopic colon cancer, subcutaneous triple-negative breast cancer, subcutaneous non-small cell lung cancer, subcutaneous and orthotopic intracranial glioblastoma, and immunocompetent lymphoma transgenic mouse models. ONC201 exhibits promising anticancer activity that has been demonstrated in a wide range of malignancies in preclinical models (e.g. glioblastoma multiforme, triple-negative breast cancer, colorectal cancer and non-small cell lung cancer) that include subcutaneous, orthotopic, and transgenic models. Beyond solid tumors, ONC201 has also demonstrated striking efficacy in tumor types such as multiple myeloma, including cells with bortezomib resistance, that are highly sensitive to induction of ER stress. Therefore, the development of ONC201 will be broad given the current need for new treatment options and the wealth of preclinical information that was generated in preclinical settings in various disease settings with the study drug.

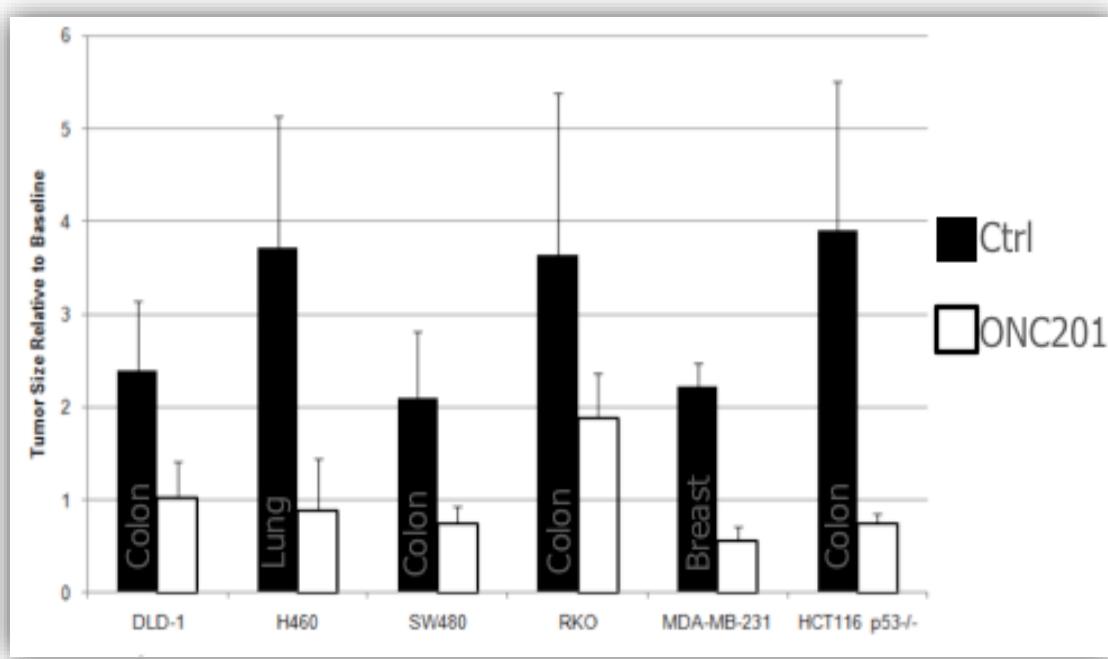


Figure 1: ONC201 antitumor activity in subcutaneous xenografts.

Subcutaneous xenografts in athymic nude mice receiving a single dose of ONC201 (100 mg/kg, IP). Data shown is approximately 1 week following single dose administration and is relative to the tumor size on the day of administration.

Preclinical efficacy studies revealed that ONC201 has peak efficacy when administered at 25 mg/kg orally once every two weeks. To begin to estimate the safety margin of ONC201 *in vivo*, exploratory exaggerated dosing studies were conducted in mice. ONC201 was administered IP to cohorts of mice as a single dose either as an IP bolus or fractionated IP dose. The single bolus dose was well tolerated up to 220 mg/kg. At 250 mg/kg, single rapidly administered IP doses of ONC201 caused labored breathing, dyspnea, and death. A dose of 250 mg/kg ONC201 administered IP and divided into four equivalent doses was well-tolerated. The preclinical efficacy of ONC201 in mice was achieved at doses as low as 12.5 mg/kg with maximal efficacy observed in at least one model at 25 mg/kg. Administering ONC201 twice a week in nude mice at 25 mg/kg caused a mild reversible skin rash following two weeks of administration that was not observed with weekly administration.

2.1.2.2 Mechanism of Action (MOA)

ONC201 was identified through a phenotypic screen as a small molecule that induces p53-independent upregulation of TRAIL gene transcription in tumor cells. A series of gene expression profiling and cell signaling investigations have unraveled signaling pathways that are engaged in tumor cells following ONC201 treatment.

ONC201 appears to activate the integrated stress response (ISR), which is the same signaling pathway activated by ER stress-inducing compounds such as proteasome inhibitors (e.g. bortezomib). When the ISR is activated by ER stress-inducing compounds, the pathway is often referred to as the ER stress response. ONC201 causes an early-stage increase in the phosphorylation of eIF2-alpha at serine 51, which results in attenuation of protein translation and upregulation of the transcription factor ATF4 (Figure 2: Proposed model of ONC201 MOA in tumor cells). ATF4 up regulates CHOP, which is also a transcription factor that regulates several apoptosis-related genes such as the TRAIL-receptor DR5. ATF4 and CHOP upregulate expression of TRB3, which interacts directly with Akt to decrease its kinase activity. TRB3 also serves as a scaffold protein in the MAPK signaling pathway that can negatively regulate this pathway. Decreased levels of phospho-MEK, -ERK, and -Akt have been documented in response to ONC201. The decreased ERK and Akt kinase activity results in less phosphorylated Foxo3a, which is a transcription factor that regulates both the TRAIL and DR5 genes. Dephosphorylated Foxo3a undergoes nuclear translocation and activation in response to ONC201.

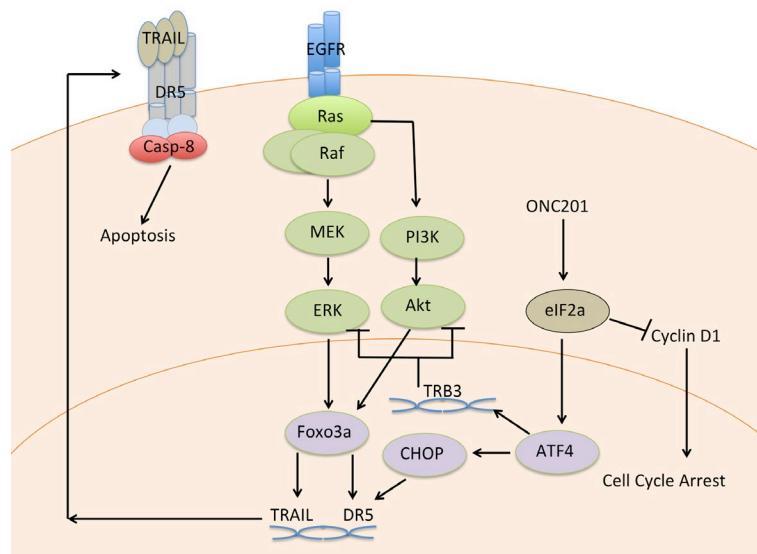


Figure 2: Proposed model of ONC201 MOA in tumor cells

In summary, ONC201 appears to activate the ISR that attenuates protein translation and activates ATF4, which causes induction of genes that lead to apoptosis. ATF4 and CHOP also downregulate Akt and ERK activity that cooperatively induce complementary downstream apoptotic effects. Preliminary evidence suggests that ONC201 may not activate eIF2-alpha through PERK. This distinct mechanism may explain the lack of cross-resistance between ONC201 and other ER stress-inducing agents such as bortezomib. In addition, ONC201 has enhanced antitumor efficacy in combination with bortezomib that may be explained by engaging parallel stimuli that lead to an enhanced activation of the ISR in tumor cells.

ONC201/TIC10 inhibition of Akt and ERK oncogenic pro-survival kinases leads to Foxo3a and TRAIL gene transactivation and toxicity to freshly isolated patient-derived CRC cells

We discovered that ONC201, as a single chemical entity, is a dual inhibitor of p-Akt and p-ERK in human CRC cell lines (Figure 3; Allen et al., 2013). The inhibition of Akt and ERK leads to dephosphorylation of Foxo3a on different target sites for these kinases (Figure 3), nuclear translocation of Foxo3a (Allen et al., 2013, and direct transcriptional upregulation of the TRAIL gene both in cell lines and *in vivo* (Allen et al., 2013).

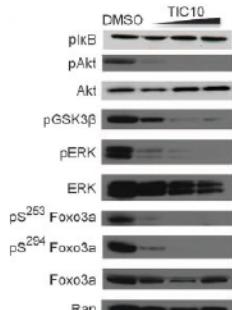
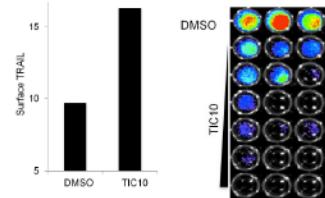


Figure 3. ONC201/TIC10 is a dual inhibitor of Akt and ERK pro-survival kinases to induce TRAIL through Foxo3a. Western blot analysis of HCT116 p53-/- cells treated with ONC201/TIC10 (2.5, 5, and 10 μ M) for 72 hours. Additional experimental details as well as more detailed analysis of Foxo3a and TRAIL in additional cell lines can be found in Allen et al., 2013.

ONC201 stimulates TRAIL production on the cell surface and displays toxicity towards fresh human CRC cells (Figure 4; Allen et al., 2013). We have demonstrated that Foxo3a and TRAIL are critical to the anti-tumor effects of ONC201 both in cell culture and *in vivo* (Allen et al., 2013).

Figure 4. ONC201 stimulates TRAIL expression on the cell surface and displays toxicity towards freshly isolated human CRC cells. Panel 4A (left panel). ONC201/TIC10-induced cell surface TRAIL expression in freshly resected colon cancer cells (10 μ M, 72 hours). Data are expressed as median fluorescence intensity. All primary patient specimens were obtained in accordance with IRB-approved protocols. Samples were received immediately after resection, manually digested in complete DMEM media, filtered with a 100- μ m nylon mesh, and plated at 2×10^5 cells/ml in complete DMEM. Panel 4B (Right Panel). Cell viability assay of primary colon cancer cells from panel A treated with DMSO, ONC201/TIC10 (0.6, 1.25, 2.5, 5, 10, and 20 μ M from top to bottom).



ONC201/TIC10 induces an integrated stress response involving ATF4 and CHOP leading to upregulation of TRAIL death receptor 5 (DR5) on tumor cells. We further uncovered a critically important aspect of the mechanism of action of ONC201 that appears to be mediated through a PERK-independent integrated stress response (Kline et al., Sci. Sig., in press, 2016). Our experiments revealed that ONC201 induces ATF4 and CHOP (Figure 5) and that dual knockdown of ATF4 and CHOP inhibits the upregulation of DR5 on the surface of human CRC cells (Figure 5). Further experiments demonstrated that ONC201 effects are mediated through the eIF2-alpha kinases PKR and HRI that are required for ATF4 induction by ONC201 (Kline et al., Sci. Sig., in press, 2016).

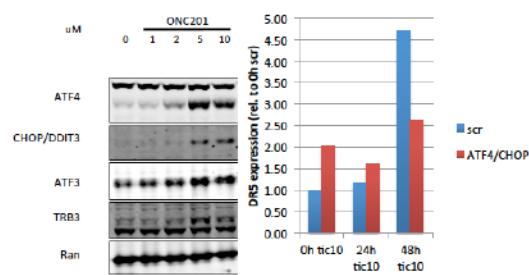
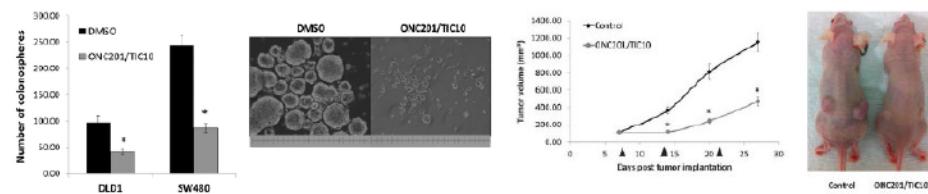


Figure 5. ONC201/TIC10 induces an integrated stress response involving ATF4 and CHOP.

Panel 5A (Left Panel). HCT116 colorectal cancer cells were treated with indicated concentrations of ONC201 for 24 hours. Western blot analyses of ATF4 and ATF4 transcriptional targets were performed. Results indicate ONC201-induced ATF4 pathway upregulation. Panel 5B (Right Panel). HCT116 cells were transfected with scrambled (scr) or ATF4 and CHOP siRNA for 24 hours. Subsequently, cells were treated with 5 μ M ONC201 and RNA was isolated from the cells after indicated treatment periods (0, 24, or 48 hr). qPCR analyses for DR5 mRNA (normalized over GAPDH mRNA) expression were performed. Bars indicate relative expression of DR5 in treated cells versus cells that were transfected with scrambled siRNA (scr) and were treated only with vehicle. Results indicate that ONC201-induced DR5 mRNA expression is dependent on ATF4/CHOP.

ONC201/TIC10 inhibits CRC stem cells, colonosphere growth and CRCs initiated by cancer stem cells (CSCs) in vivo in mice. Given the importance of CSCs to tumor relapse and drug resistance, we investigated whether ONC201 can impact on CSC-like cells in CRC models. Our results revealed that ONC201 suppresses CSC-like cells (both ALDH+ and CD133+) in cultured CRC cell lines whereas 5-FU does not (Prabhu et al., 2015). We further showed that ONC201 inhibits CRC colonosphere growth and suppresses tumor growth following implantation of sorted CRC stem cells in vivo in mice (Figure 6; Prabhu et al., 2015).



colonosphere growth and CRCs initiated by cancer stem cells (CSCs) in vivo in mice. Panel 6A (Leftmost Panel). ONC201/TIC10 prevents colonosphere formation. DLD1 and SW480 cells (10,000 cells/well) were plated for colonosphere formation in the presence of DMSO or 10 μ M ONC201/TIC10. Colonospheres ($> 60 \mu$ m) were counted at 96 h. Panel 6B (Second Panels from Left). Representative image (10X magnification) for DLD1 cells in panel 6A. Each division on the scale is 10 μ m. Panel 6C (Third Panel from Left). ONC201/TIC10 prevents CSC-mediated xenograft tumor growth. Sorted DLD1 Aldefluor(+) cells were subcutaneously injected into the right and left flank of athymic nude mice. Upon tumor formation, mice were administered either vehicle or ONC201/TIC10 50 mg/kg (i.p.). (N = 7 per group) Doses (indicated by triangle) were administered post-tumor implantation on day 7, 14 and 22. Tumor growth was monitored weekly until the endpoint. Data is presented as mean \pm standard error of mean. * indicates p < 0.05. Panel 6D (Rightmost Panels).

ONC201 preclinical dose intensification demonstrates potent anti-tumor and anti-metastasis effects in mouse models leading to design of a dose intensification trial. Given the observed safety of ONC201 in the FIH trial, we investigated whether increased dose and frequency of drug administration might enhance anti-tumor efficacy. We found evidence that increasing drug dosing from 25 to 50 and to a 100 mg/kg enhanced anti-tumor efficacy (Figure 7).

Figure 6.
ONC201/TIC10 inhibits CRC

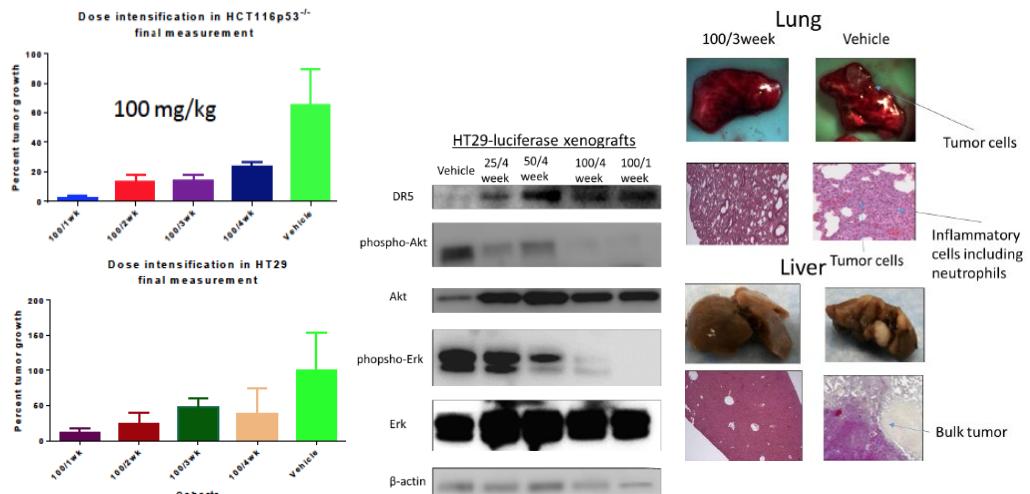


Figure 7. ONC201 preclinical dose intensification demonstrates potent anti-tumor and anti-metastasis effects in mouse models. ONC201 exerts a frequency-of-dose effect when administered at 100 mg/kg during various timelines. Six-week old female athymic nude mice were inoculated with 1.5×10^6 of HCT116 p53^{-/-} cells (upper graph) or HT29 (lower graph) in panel A (Leftmost Panels). The middle panel (Panel B) shows western blot results demonstrating partial or more complete pathway signaling suppression depending on dose intensity as indicated or as a function of more frequent dosing (tumors were harvested at 4 weeks). The right most panel (Panel C) shows metastasizing HT29-luc (bioluminescence imaging not shown). Mice were injected in both flanks and tumors were allowed to grow to $\sim 175 \text{ mm}^3$ volume before being treated with ONC201. Tumor volume was assessed through caliper measurements every 3 days and monitored by bioluminescence imaging every week (bioluminescence imaging not shown). The percent tumor growth was established based on final volume of the vehicle-treated mice. HT29 xenograft-bearing mice were sacrificed at 30 days, and HCT116 p53^{-/-} xenograft-bearing mice were sacrificed when tumor volume reached 20 mm in diameter or at 10 weeks. Histology and Hematoxylin-Eosin staining was confirmed by pathologist. (N=6 tumors, 2 tumors per each of 3 mice per cohort).

2.1.2.3 Preclinical rationale for combination of ONC201 with Opdivo (Nivolumab)

ONC201 induces CD3+/NK cell accumulation

We have noted what we consider to be an interesting observation that ONC201-treated tumors appear to contain an NK/CD3⁺ cellular infiltration, and that NK cell accumulation can be detected in the peripheral blood of ONC201-treated mice (Figure 8).

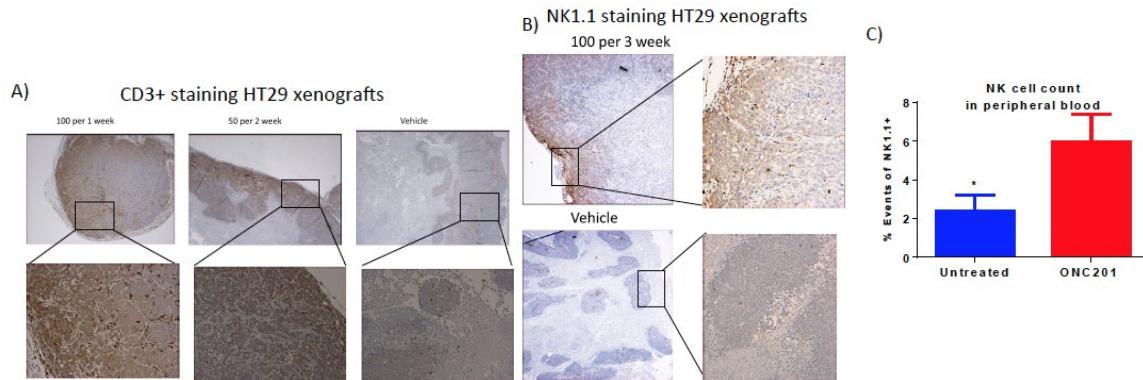


Figure 8. ONC201 induces CD3+/NK cell accumulation. A) CD3+ staining using mouse/human CD3+ in athymic nude mice. The mice were inoculated with 1.5×10^6 HT29 CRC cells and were treated with ONC201 at the doses indicated in mg/kg per 1 week or 2 weeks as indicated. Mice were treated when the xenografted tumors were 200 mm^3 and they were sacrificed on day 35. Tumors were harvested and embedded in paraffin, sectioned and stained as described. B) NK1.1 IHC staining using mouse specific NK1.1 (PK136) antibody in athymic nude mice. The mice were inoculated as described in panel A, but the example shown here they were treated with 100 mg/kg of ONC201 every 3 weeks and tumors were again harvested at 35 days. C) Flow cytometry analysis of NK1.1 cells in untreated and ONC201 (100 mg/kg) C57/BL6 mice through orbital bleed performed in a non-tumor bearing mouse. Blood was sampled at 24 hrs after drug administration. Dead cells and CD11b cells (B-cells) were gated out from this analysis.

Potent CRC growth inhibition in mice from combination of ONC201 and anti-PD1
 The combination of ONC201 with anti-PD-1 therapy resulted in more potent in vivo tumor suppression with the combination versus anti-PD-1 therapy alone (Figure 9).

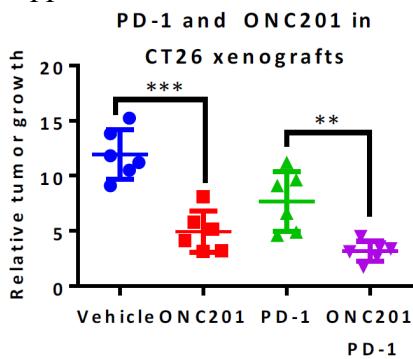


Figure 9. ONC201 in combination with anti-PD1. Relative tumor volume after 4 weeks in CT26 tumors in Balb/c mice treated with vehicle, 100 mg/kg ONC201, anti-PD-1, or ONC201 + anti-PD-1.

2.1.2.4 Nonclinical Safety/Toxicology Studies in Animals

In rats and dogs ONC201 was better tolerated when administered orally compared to intravenously. In rat non-GLP studies, the No-Observed Adverse Effect Level (NOAEL) was 225 mg/kg with oral administration compared to 100 mg/kg with a 2 hour infusion and 50 mg/kg with

a 30 minutes infusion. Non-GLP clinical observations in rodents included decreased activity, altered gait, and mortality. In dog non-GLP studies, the NOAEL in doses was at least 120 mg/kg with oral administration and clinical observations were limited to emesis and changes in fecal consistency. The non-GLP studies only evaluated clinical observations, weight gain, food consumption and gross findings at necropsy. In general, the toxicology/safety studies indicate that the acute toxicities associated with ONC201 are limited to the day of administration and are reversible.

In GLP dog studies, the NOAEL was at least 42 mg/kg. Observations were limited to decreased activity, decreased food consumption, emesis, salivation, and/or soft, stool or mucous feces. In rat GLP studies, the NOAEL was at least 125 mg/kg. Observations included decreased activity, decreased food consumption, decreased body weight, and abnormal stance and gait. Minor changes in serum chemistries were noted, largely in the 225 mg/kg rat cohort, which included slight increases in cholesterol and chloride. The significance of these findings is unknown as other clinical chemistry and histology did not corroborate this observation (e.g. liver findings). Rats receiving 125 or 225 mg/kg ONC201 had mild edema and inflammation that was primarily submucosal in the stomach and was completely resolved by day 19.

2.1.2.4.1 Non-GLP Safety Studies

Non-GLP studies were conducted in rats and dogs to assess clinical observations and body weight with ONC201.

Non-GLP toxicology studies in rats

The ability of rats to tolerate ONC201 by intravenous administration was explored as a function of infusion time. Clinical observations with intravenous administration included decreased activity, salivation, abnormal gait and stance, labored respiration, pale skin, nasal discharge, prostration during the dose, mild body twitching, and red discharge from the mouth.

The NOAEL following administration of ONC201 to Sprague-Dawley rats by a 30-minute intravenous infusion was 50 mg/kg. The NOAEL following administration of ONC201 to Sprague-Dawley rats by a 2-hour intravenous infusion was 100 mg/kg. Administration of 100 mg/kg ONC201 by intravenous infusion over 30 minutes resulted in the death of one male rat. Administration of 200 mg/kg ONC201 by a 2-hour infusion resulted in the death of both animals during the infusion period. Following these observations, the tolerance of oral ONC201 was explored given the potential to lower acute toxicity by lowering the maximal concentration (C_{max}). Clinical observations with oral exaggerated doses of ONC201 included decreased activity, abnormal gait and stance, prostration, irregular respiration, moderate twitching, red discharge on the muzzle, scant feces, hunched posture, not eating, piloerection, and skin cold to touch. The NOAEL following administration of ONC201 to Sprague-Dawley rats by oral gavage was 225 mg/kg.

Non-GLP toxicology studies in dogs

In parallel to non-GLP toxicology studies in rats, the ability of beagle dogs to tolerate ONC201

was explored. No deaths were observed at any doses in dogs. The NOAEL following the 30-minute intravenous infusion of ONC201 to beagle dogs is considered to be at least 33.3 mg/kg. The 2 hour-intravenous infusion of 16.7 mg/kg ONC201 was not associated with any clinical signs of toxicity. Therefore, the NOAEL following a 2 hour-intravenous infusion of ONC201 to beagle dogs is considered to be greater than 16.7 mg/kg, though higher doses were not explored as the oral route was selected for further development based on observations in rats. The NOAEL with oral ONC201 was considered to be at least 120 mg/kg in dogs. Clinical observations at doses of 66.7 to 120 mg/kg were limited to emesis and changes in fecal consistency.

2.1.2.4.2 GLP Toxicology and Safety Studies

Single Dose Oral Toxicity Study in Dogs (GLP)

A GLP study was performed to evaluate the toxicity and toxicokinetics of ONC201 following a single oral dose to Beagle dogs followed by a 2-day or an 18-day recovery period. Dogs received a single dose of 0, 4.2, 42, or 120 mg/kg by oral gavage. There was no mortality observed in this study. There were no definitive ONC201-related effects on group mean body weight or body weight gain, EKG rhythm or morphology, mean heart rate or arterial blood pressure, urinalysis, hematology parameters, coagulation parameters, clinical chemistry parameters, erythrocyte morphology, gross findings on necropsy, changes in absolute or organ to body or organ to brain weights.

Although not statistically significant, there were some dose-related decreases in group mean food consumption for the first week following dosing. The 120 mg/kg females had statistically significantly decreased group mean food consumption compared to the vehicle control group on Days 14, 15 and 18. There were no clinical signs of toxicity noted following a single dose of 4.2 mg/kg ONC201. At a dose of 42 mg/kg and 120 mg/kg, some dogs had clinical observations at approximately 1-hour post-dose including decreased activity, emesis, salivation, and/or soft, loose or mucous feces. Of uncertain relationship to ONC201 administration was the unusual finding of mononuclear cell inflammation in the blood vessels of the brain, which was multifocal and mild in one high dose female at Day 3, multifocal and minimal in one high dose female at Day 19, and minimal and focal in one control female at Day 19. Similar findings were not noted in any male animal.

Based on the results of this study, the NOAEL following oral administration of ONC201 at single doses of 4.2, 42 or 120 mg/kg to Beagle dogs is considered to be at least 42 mg/kg.

Single Dose Oral Toxicity and Toxicokinetic Study in Rats with a 19-Day Recovery (GLP)

A GLP study was performed to evaluate the toxicity of ONC201 following a single oral dose in Sprague-Dawley rats with necropsy after a 2-day or an 18-day recovery period. Rats received 0, 12.5, 125, or 125 mg/kg ONC201 by oral gavage.

There was no mortality observed in this study. There were no definitive ONC201-related effects on coagulation parameters, clinical chemistry parameters, gross findings at necropsy. There were no clinical signs of toxicity noted at single doses up to 125 mg/kg ONC201. There were no ONC201-related statistically significant changes in hematology parameters or clinical chemistries

outside of the historical control range for these values.

At a dose of 225 mg/kg, clinical signs of toxicity were limited on the day of dose administration to one out of twenty males and one out of twenty females that showed signs of decreased activity and abnormal gait and stance. The male was also noted to have increased respiration. All were normal by Day 2. No ONC201 related changes were noted during the functional observational battery (CNS activity) performed on Day 1 between 1 and 2 hr post-dose with the exception of one 225 mg/kg female noted as having decreased activity. A statistically significant decrease in group mean body weight gain was noted on Day 7 for the 225 mg/kg males. A statistically significant decrease in group mean food consumption was noted on Day 7 for the 225 mg/kg males.

On Day 3 the 225 mg/kg females also had increased glucose, cholesterol, sodium and chloride. Sodium and chloride were statistically significantly increased for the 125 mg/kg females. Only cholesterol and chloride were outside historical control ranges for this laboratory on day 19. As the increase in cholesterol was only noted for the females and no corresponding liver findings were observed, the significance of this finding is unknown. Though within normal historical control values for these laboratories, chloride remained increased for the 225 mg/kg males while cholesterol remained increased for the 225 mg/kg females.

Changes in brain and liver weights were noted but did not occur in a dose-dependent manner and no microscopic changes were noted for in these organs for the high dose females. These changes were considered incidental and unrelated to treatment. At the Day 3 necropsy, ONC201-related minimal to mild edema and/or mixed cell inflammation was present in the non-glandular stomach of 225 mg/kg males and females. This edema and inflammation was primarily submucosal, although in some animals the inflammation involved the serosa or mesentery. Two males and one female had minimal focal ulceration of the overlying squamous epithelium. Similar stomach findings were seen in 125 mg/kg animals, with a lower incidence than in 225 mg/kg. There was complete resolution of all stomach lesions at the Day 19 necropsy, indicating full recovery.

Based on the results of this study, the NOAEL following oral administration of ONC201 at single doses of 12.5, 125 or 225 mg/kg to Sprague-Dawley rats is considered to be at least 125 mg/kg.

Evaluation of the Effect of ONC201 Dihydrochloride on Respiratory Function Following Single-Dose Administration in Rats (GLP)

A GLP study was performed to determine the potential effects of ONC201 dihydrochloride on respiratory function in rats following a single oral gavage administration. Twenty-four (6/group) male rats received 0, 12.5, 125, or 225 mg/kg ONC201 by oral gavage and were monitored in plethysmographic chambers. The oral administration of ONC201 dihydrochloride at 12.5 and 125 mg/kg did not induce any biologically relevant effects on respiratory rate, tidal volume or minute volume in conscious male rats. A marginal to moderate transient decrease in respiratory rate and minute volume was observed following the oral administration of ONC201 dihydrochloride at 225 mg/kg, which resolved by 2 hours.

2.1.2.5 Pharmacokinetic Studies

The measured half-life of ONC201 in mice is ~6 hours with intravenous administration as measured by an HPLC-UV assay. In rats, exposure to ONC201 was dose-dependent and approximately dose-proportional. Exposure to ONC201 was slightly greater in female rats after a single oral gavage dose. Plasma $t_{1/2}$ ranged from 2.3 to 8.4 hours in 7 of 8 profiles. Clearance ranged from 7.5 to 23.5 L/hr/kg in 7 of 8 profiles. Volume of distribution ranged from ~49 to ~103 L/kg in 6 of 8 profiles.

In dogs, exposure to ONC201 following oral gavage dosing at 4.2, 42, and 120 mg/kg ONC201 was dose-dependent and increased with greater ONC201 dose levels. Exposure to ONC201 was similar in male and female dogs with the observation that all mean male C_{max} and AUC values were slightly greater than those corresponding female values. Elimination of ONC201 from plasma was similar between the mid and high dose levels; mean $t_{1/2}$ ranged from 4.6 to 7.8 hours. Mean $t_{1/2}$ following the low dose of 4.2 mg/kg was ~1 hour [the half-life determined for dogs in the low dose group may represent more of a distribution phase half-life rather than the terminal plasma elimination half-life]. Overall elimination of ONC201 was greater following the low dose.

In a Phase I dose-escalation clinical trial of ONC201 in patients with advanced solid tumors, the pharmacokinetics of single agent ONC201 was determined by LC-MS-MS analysis of plasma collected in the first cycle of therapy within 21 days of drug administration (Fig 2.3). While dose escalation involved single patient cohorts, systemic exposure to ONC201, as determined by AUC and C_{max} , appeared to saturate at a dose of 375 mg. PK parameters are summarized for patients who received the RP2D in Table 2.1. For the top dose cohort, the mean C_{max} was 3312 (SD 2133) ng/mL, which occurred on average 1.8 hours following administration. The mean V_z was 381 (SD 164) L, consistent with a large distributive volume. Mean AUC was 26.3 (SD 10.8) h. μ g/mL, and mean CL/F was 27.19 (SD 10.95) L/h. The mean $t_{1/2}$ was 9.62 (SD 1.76) hours.

	C_{max} (ng/mL)	T_{max} (h)	T_{lag} (h)	AUC_{last} (h.ng/L)	λ_z (h ⁻¹)	$t_{1/2}$ (h)	AUC (h.ng/m)	V_z/F (L)	CL/F (L/h)
N	6	6	6	6	6	6	6	6	6
Mean	3312	1.79	0.05	25515	0.074	9.62	26344	381	27.19
SD	2133	1.30	0.12	10677	0.013	1.76	10763	164	10.95
Min	1530	0.37	0.00	13490	0.055	7.71	13868	156	14.03
Median	2725	1.91	0.00	24265	0.072	9.60	25620	404	24.83
Max	7470	3.95	0.30	43830	0.090	12.55	44555	616	45.07
CV%	64.4	72.4	244.9	41.8	17.4	18.3	40.9	42.9	40.3
Geo. Mean	2894	1.34	.	23777	0.073	9.49	24601	348	25.41
Geo. CV%	58.0	113.5	.	42.9	18.0	18.0	42.4	52.9	42.4

Table 1: Mean ONC201 pharmacokinetic parameters determined in patients receiving 625 mg ONC201 every three weeks

Generally, CL/F was observed to be variable but consistent across all the dose groups. There were no apparent relationships between drug CL/F and patient sex and age. Noticeable, shallow trends were observed with patient weight and BSA. An overall increase in CL/F was observed as weight and BSA increased. Although a slight upward trend was observed, there was no strong correlation between CL/F and CLCR.

Stronger correlations were observed with the distributive volume estimate (VZ) and patient weight and BSA. A pronounced increase in VZ was observed with increasing patient weight. A greater than 2-fold increase in VZ is predicted from this trend with an increase in weight from 50 to 100 kg. A similar trend was observed between VZ and BSA. Trends of decreasing exposure with increasing weight were observed in plots of Cmax/Dose and AUC/Dose versus patient weight. Weight normalized CL/F was plotted versus dose, showing a similar trend to un-normalized CL/F, but with significantly less variability across patients in the 625 mg dose group.

2.2 Clinical Studies

2.2.1 Safety of ONC201

The clinical safety of ONC201 has been evaluated in a Phase I clinical trial; An open-label, dose-escalation Phase I trial of single agent ONC201 was conducted in patients with advanced refractory solid tumors who had exhausted or refused standard treatment options. The primary objective of this study was to determine the maximal tolerated dose (MTD) and to determine the recommended Phase II dose (RP2D) of oral ONC201 and to evaluate the safety and tolerability of the drug. Secondary objectives were to study the pharmacokinetics and pharmacodynamics of ONC201 and preliminary assessment of anti-tumor efficacy.

An accelerated dose escalation design was used to reduce the number of patients treated at potentially sub-therapeutic dose. Ten evaluable (aged 47-80 years) patients received oral ONC201 once every 3 weeks at five dose levels ranging from 125 to 625 mg. The study design included only one patient per cohort until any patient experiences a grade 2 adverse event during the first cycle of treatment, defined as 21 days. Five dose levels (125 mg, 250 mg, 375 mg, 500 mg, 625 mg) were evaluated. Enrollment at each subsequent dose level required that all patients enrolled at the prior dose level completed Cycle 1 dosing and were evaluated 21 days later to assess safety and had no grade toxicity.

On average, patients received 3.1 doses of ONC201. Nine out of ten patients completed at least 2 cycles, 4 patients completed at least four cycles, and one patient received six cycles and remains on therapy. 625 mg was the highest dose administered and was determined to be the RP2D that surpassed the absorption saturation threshold by two dose levels. The only adverse event during the dose escalation phase that was possibly attributed to ONC201 was a low-grade fever. No Grade >1 drug-related toxicities were observed. Explorative laboratory studies and physical exams did not reveal any drug-related abnormalities. Similarly, cardiovascular assessments revealed no drug-

related effects. (Stein MN et al. Clin Cancer research 2017)

Clinical efficacy was observed in some patients; Patient #3, a 72-year-old with advanced clear cell endometrial cancer, had a mixed objective response with >50% decrease in lymphadenopathy (10/11 afflicted lymph nodes responded) after 2 doses. Patient #4, a 62-year-old male with renal cancer and bone metastases with debilitating pain in the clavicle, experienced relief from his clavicular pain. Patient #6, a 69-year-old patient with prostate adenocarcinoma, has received 8 doses of ONC201 and has stable disease. Patient #8, a 71-year old colon cancer patient had stable disease for at least 12 weeks with 4 doses of ONC201 (Figure 10).

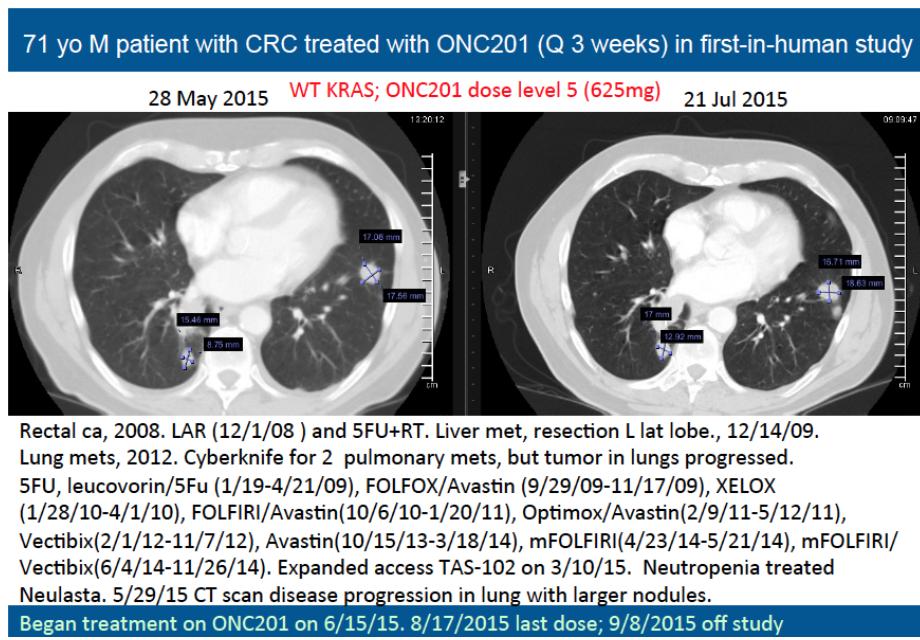


Figure 10. Stable disease over 12 weeks in the patient with mCRC who received Q 3-week ONC201 in first-in-human study.

A 47-year-old male with appendiceal cancer (patient #2) had biochemical response with CA27.29 declining from 30 units to 20 units (normal range) after 4 doses of ONC201. Given the heterogeneity of the tumor types in the enrolled patients, no widely used biomarker was available to uniformly assay all patient samples. Since most solid tumors express cytokeratin-18, the serum M30 assay was selected to detect a caspase-cleaved form of cytokeratin-18 (Demiray et al; 2006). Induction of the M30 assay for apoptosis was noted in 67% of patients treated at the RP2D with a range of 1.25- to 4-fold increase.

Eighteen patients were enrolled in the expansion phase, patients received 625mg of ONC 201 orally every 3 weeks. On the basis of these clinical observations in the dose escalation phase, the expansion phase enriched for endometrial and prostate cancer patients. A 90-year-old prostate

cancer patient had a rapid shrinking of his primary tumor and metastatic bone lesion (~25%) after two doses of 625 mg ONC201. Waterfall analysis of the 28 patients on a lesion-by-lesion basis revealed tumor regressions in prostate and endometrial cancer patients that involved lymph nodes, bone, and lung lesions). An endometrial cancer patient experienced stable disease for 42 weeks and exhibited sustained regression of her metastatic lung lesion. The only adverse events among these 18 patients that were attributed as possibly related to ONC201 were nausea in 1 patient, emesis in 1 patient, and increased serum amylase in 2 patients. All of these adverse events were grade 1 and reversed rapidly. In a phase II study of ONC 201 in patients with recurrent glioblastoma was recently reported. Seventeen patients with recurrent, bevacizumab-naïve, IDH1/2 WT glioblastoma were enrolled. Patients received 625mg ONC201 every three weeks. Median OS was 41.6 weeks with OS of 71% and 53%. At 6 and nine weeks respectively. Seven of 17 patients are alive. PFS6 was 11.8% with two patients remaining on study who continue to receive ONC201 for >12 months. One of these patients had a durable objective response with a secondary glioblastoma possessing a H3.3 K27M mutation, exhibiting regression by 85% in one lesion and 76% in the second lesion. The second patient who continues to receive ONC201 for >12 months remains disease-free after enrolling on this trial following a re-resection. No drug-related SAEs or treatment discontinuation due to toxicity occurred. Plasma PK at 2 hours' post-dose was 2.6 ug/mL, serum prolactin induction was observed as a surrogate marker of target engagement, and DRD2 was expressed in all evaluated archival tumor specimens. (Arrillaga-Romany I et al. oncotarget)

Additional clinical studies of ONC201 are currently enrolling or being initiated, including a Phase I clinical trial in multiple myeloma, a Phase I/II trial in relapsed/refractory acute leukemias and high-risk myelodysplastic syndrome, a Phase I/II trial in advanced non-Hodgkin's lymphoma

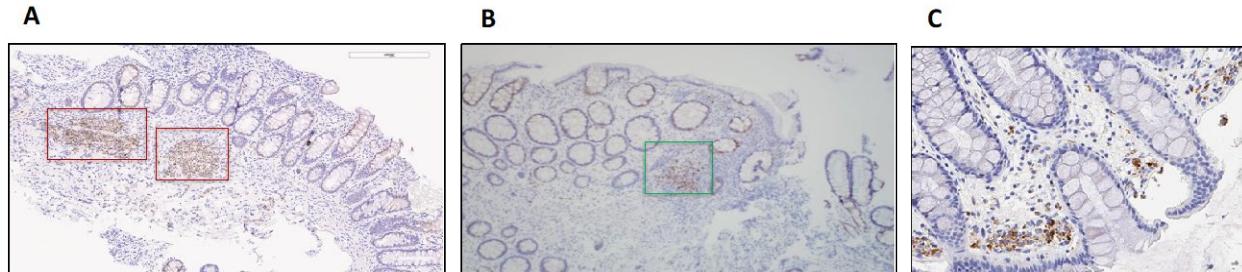
In a currently enrolling phase II study of ONC 201 in patients with relapsed NHL, the first patient treated with ONC201 had relapsed/refractory mantle cell lymphoma with gastrointestinal manifestations; after the first post-treatment evaluation, patient had a striking response with almost complete eradication of disease (Figure 11). After only two doses of 125mg ONC201 (1/5th of the RP2D) spaced three weeks apart, the tumor disappeared from the colon and only small foci of residual disease were found on rectal biopsy. DRD2 expression was detected at baseline biopsy. Patient continue to be in complete remission based on recent endoscopy. Additionally, a 22-year old patient with recurrent glioblastoma (unmethylated MGMT, H3.3 mutant) had a confirmed objective response with 625 mg ONC201 every three weeks resulting in an 82% reduction in overall tumor size and continues treatment with a durable response for over 1 year (Figure 12). Peripheral blood samples from patients who received ONC201 treatment showed a 2-10 fold increase in the number of activated TRAIL-secreting NK cells after ONC201 treatment up to three days after treatment (Figure 13).

Figure 11: Rectal biopsy of relapsed/refractory MCL patient with cyclin D1 at (A) baseline
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Dates: 11/04/2018, 11/11/18, 11/16/18, 11/24/18, 11/30/18, 12/2/18, 12/6/18, 12/7/18, 12/10/18, 1/8/19 BMS review, 1/9/19, 1/13/19, 1/15/19, 1/16/19, 1/17/19, 1/20/19, 1/22/19, 2/4/19, 2/19/19, 3/19/19, AM#1 7/22/19, BMS review 8/23/19, AM#2 3/3/20, BMS approved 4/1/20, Oncoceutics approved 4/24/20, AM#3 10/26/2020, BMS approved 1/5/21, Oncoceutics approved 3/30/21



and (B) after 3 doses of 125mg ONC201 once every 3 weeks. DRD2 expression at baseline in rectal biopsy shown in (C). Patient currently in complete remission based on recent endoscopy.

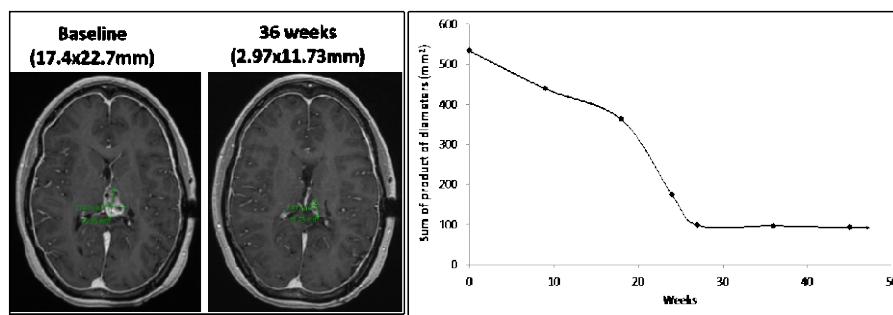


Figure 12: Partial response in recurrent glioblastoma patient with 625mg ONC201

every 3-weeks.

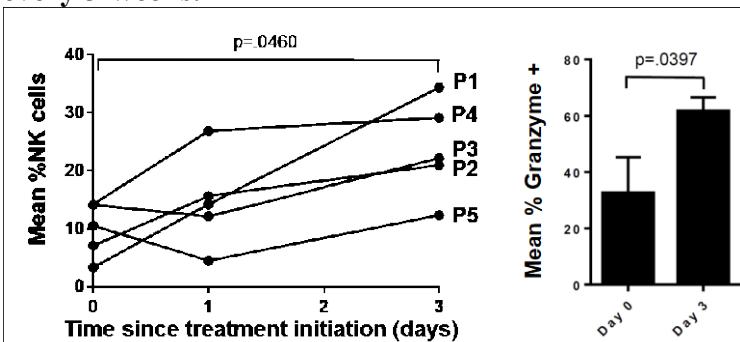
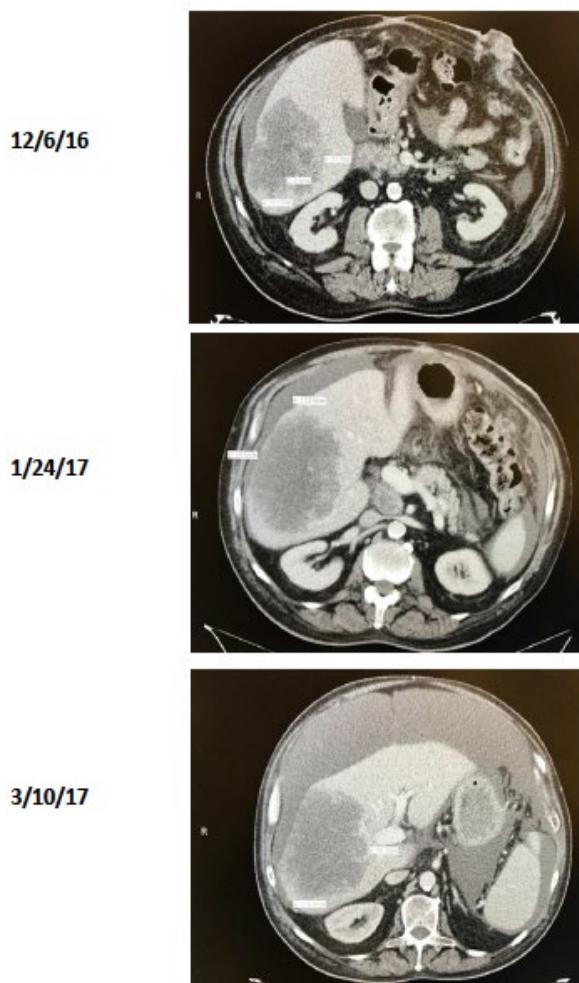


Figure 13: NK cells are increased in peripheral blood of patients following treatment with ONC201. Percentage of NK cells in PBMCs (left) and percentages of NK cells expressing Granzyme B (right) following 625 mg weekly ONC201 administration.

In addition, a 68-year-old male with advanced colon cancer was treated with 375 mg ONC201 on an every 3-week schedule.

Another 68-year-old patient with metastatic KRAS/NRAS wild type, APC and p53 mutant colon cancer who progressed on 3 lines of therapy was treated with ONC201 monotherapy at 625 mg PO Q 3 weeks



68 yo M with mCRC, KRAS/NRAS WT, APC and p53 mutant tumor.
Prior FOLFOX/Avastin 7/15, FOLFIRI/Cetuximab 2/16, Lonsurf 8/16

Lesion	Location	12/6/16	1/24/17	Trend 1/24	3/10/17	Trend 3/10
		Q3 week ONC201	Off ONC201 therapy			
1	Lung: RUL	0.5	0.8 x 0.5	Increase	0.8 x 0.8	SI increase
2	Liver: segment 8		0.7		1.2	SI increase
3	Liver: segment 8				0.5	New
4	Liver: segment 8/7	2.2 x 1.9	3.5 x 2.7	Increase	3.1 x 1.9	Decrease
5	Liver: segment 2		2.6 x 1.5		2.2 x 1.5	Decrease
6	Liver: inferior lobe	10.2 x 7.8	12.4 x 8.7	Increase	12 x 8.5	Stable
7	Liver: segment 6		2.9 x 2.3		2.9 x 2.6	Stable
8	Superior Portacaval Node		3.8 x 3.0		2.9 x 3.1	Decrease
9	Inferior Portacaval Node	3.0 x 3.5	4.1 x 3.1	Increase	3.6 x 2.6	Decrease
10	Serosal implant: Transverse colon		1.5 x 1.6		2.1 x 2.0	Increase
11	RLQ	4.8 x 3.0	5.2 x 2.9	Increase	5.5 x 2.7	Stable

Table 2. Mixed response in the subsequent 7 weeks after patient came off of the ONC201 trial.

Figure 14. CT scans showing initial increase in the largest lesion in patient with mCRC treated with ONC201. A subsequent CT taken ~7 weeks later before the patient had any further treatment showed stable disease. Other lesions (see Table 2) showed regression. This patient received a total of two doses of ONC201 for progressive pretreated mCRC (on a Q3 week schedule). The patient's initial staging scan suggested progressive disease and patient was taken off study on January 24. Table 2 shows 5 lesions that appeared larger on 1/24/17 vs 12/6/17.

The patient had 2 doses of ONC201 and came off-therapy because of disease progression. (Figure 14 and Table 2).

Follow up scans after treatment discontinuation surprisingly showed a continued mixed response

with some lesions that decreased (4 of 11 measured lesions) and large lesions that remained stable (3 of 11 lesions). There were some lesions that slightly increased (3 of 11 lesions) and there was one new lesion. See Table 2 for lesion sizes.

Preclinical data suggesting a potent ONC201 dose intensification effect coupled with suppression of metastases, an NK cell infiltration, and a potent preclinical tumor suppression in patients with mCRC. This supports dose intensification to potentially lead to a better response in patients with mCRC. In addition, the somewhat delayed response is consistent with the hypothesis that ONC201 has an immune stimulatory effect that may last beyond the immediate PK and PD anti-tumor effects. Further evidence for this mechanism will be pursued in the proposed clinical trial.

More recent clinical trial data in prostate cancer shows evidence of increased granzyme B in post-treatment biopsies (unpublished, Mark Stein et al.). Since tumor biopsies were not available for most patients in phase 1 ONC201 monotherapy studies, immune cytokine and effector profiling was conducted from serum samples using a multiplex cytokine (unpublished, Mark Stein et al.). A broad induction of immune cytokines and effector molecules was observed amongst patients treated with ONC201, in particular among patients who experienced at least stable disease by RECIST for 12 or more weeks. Examining the kinetics of this response revealed that maximum immune cytokine induction tended to occur within the first two cycles, while maximum effector induction tended to occur beyond cycle 2 (unpublished, Mark Stein et al.). Examination of the serum samples from previously reported patients treated on the once every three-week schedule revealed a similarly broad immune cytokine and effector molecule induction (unpublished, Mark Stein et al.). The magnitude of induction was generally lower than that of patients who received ONC201 once weekly, though this did not reach statistical significance (unpublished, Mark Stein et al.). Patients who had a >50% induction in serum perforin, a cytolytic protein found in granules of cytotoxic T lymphocytes (CTLs) and NK cells¹⁹, upon ONC201 administration had a significantly longer progression-free survival (P=0.011; HR=0.3211) (unpublished, Mark Stein et al.).

Based on the expected delayed immune response and immune stimulatory effect of intense dose ONC 201, We now propose this phase I/II study of the combination of ONC201 plus Nivolumab in patients with microsatellite stable advanced metastatic colorectal cancer.

2.2.2 Dosage and Administration of Opdivo (Nivolumab)

Based on FDA labeling and investigator brochure provided by the manufacturer dosage and administration of Opdivo (Nivolumab) for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer is 240 mg every 2 weeks administered as an intravenous infusion over approximately 30 minutes.

2.2.3 Safety of Opdivo (Nivolumab)

The clinical safety of Opdivo (Nivolumab) has been evaluated in multiple clinical trials for the treatment of multiple human cancers and is approved by FDA to be used alone or with other drugs to treat a number of pediatric and adult cancers.

Based on FDA labeling and investigator brochure provided by the manufacturer the most common adverse reactions ($\geq 20\%$) in patients as a single agent were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain.

Immune-Mediated Adverse Reactions See Appendix D

Based on FDA labeling and investigator brochure provided by the manufacturer the following adverse reactions have been reported:

- Immune-Mediated Pneumonitis
- Immune-Mediated Colitis
- Immune-Mediated Hepatitis
- Immune-Mediated Endocrinopathies
- Immune-Mediated Nephritis and Renal Dysfunction
- Immune-Mediated Skin Adverse Reactions
- Immune-Mediated Encephalitis
- Other Immune-Mediated Adverse Reactions
- Infusion Reactions
- Complications of Allogeneic HSCT after Opdivo

The below is the adverse reactions discussed in greater detail:

Immune-Mediated Pneumonitis

In patients receiving Opdivo as a single agent, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. The median time to onset of immune-mediated pneumonitis was 3.5 months (range: 1 day to 22.3 months). Immune-mediated pneumonitis led to permanent discontinuation of Opdivo in 1.1%, and withholding of Opdivo in 1.3% of patients. Approximately 89% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per

day) for a median duration of 26 days (range: 1 day to 6 months). Complete resolution of symptoms following corticosteroid taper occurred in 67% of patients. Approximately 8% of patients had recurrence of pneumonitis after re-initiation of Opdivo.

Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis.

Management

Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue Opdivo for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold Opdivo until resolution for moderate (Grade 2) pneumonitis [see Dosage and Administration].

Immune-Mediated Colitis

In patients receiving Opdivo as a single agent, immune-mediated colitis occurred in 2.9% (58/1994) of patients; the median time to onset was 5.3 months (range: 2 days to 20.9 months). Immune-mediated colitis led to permanent discontinuation of Opdivo in 0.7% and withholding of Opdivo in 1% of patients. Approximately 91% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 1 day to 9.3 months).

Four patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of Opdivo.

Management

Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

Withhold Opdivo for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue Opdivo for life-threatening (Grade 4) or for recurrent colitis upon re-initiation of Opdivo [see Dosage and Administration].

Immune-Mediated Hepatitis

In patients receiving Opdivo as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of Opdivo in 0.7% and withholding of Opdivo in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least

40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of Opdivo.

Management

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations.

Immune-Mediated Endocrinopathies

Hypophysitis

In patients receiving Opdivo as a single agent, hypophysitis occurred in 0.6% (12/1994) of patients; the median time to onset was 4.9 months (range: 1.4 to 11 months).

Hypophysitis led to permanent discontinuation of Opdivo in 0.1% and withholding of Opdivo in 0.2% of patients. Approximately 67% of patients with hypophysitis received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 5 to 26 days).

Management

Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold Opdivo for moderate (Grade 2) or severe (Grade 3). Permanently discontinue Opdivo for life-threatening (Grade 4) hypophysitis [see Dosage and Administration].

Adrenal Insufficiency

In patients receiving Opdivo as a single agent, adrenal insufficiency occurred in 1% (20/1994) of patients and the median time to onset was 4.3 months (range: 15 days to 21 months). Adrenal insufficiency led to permanent discontinuation of Opdivo in 0.1% and withholding of Opdivo in 0.5% of patients. Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy and 25% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 11 days (range: 1 day to 1 month).

Management

Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe

(Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold Opdivo for moderate (Grade 2) and permanently discontinue Opdivo for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency [see Dosage and Administration].

Hypothyroidism and Hyperthyroidism

In patients receiving Opdivo as a single agent, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients; the median time to onset was 2.9 months (range: 1 day to 16.6 months). Approximately 79% of patients with hypothyroidism received levothyroxine and 4% also required corticosteroids. Resolution occurred in 35% of patients.

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving Opdivo as a single agent; the median time to onset was 1.5 months (range: 1 day to 14.2 months). Approximately 26% of patients with hyperthyroidism received methimazole, 9% received carbimazole, 4% received propylthiouracil, and 9% received corticosteroids. Resolution occurred in 76% of patients

Management

Monitor thyroid function prior to and periodically during Opdivo treatment. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of Opdivo for hypothyroidism or hyperthyroidism.

Type 1 Diabetes Mellitus

In patients receiving Opdivo as a single agent, diabetes occurred in 0.9% (17/1994) of patients including two cases of diabetic ketoacidosis. The median time to onset was 4.4 months (range: 15 days to 22 months).

Management

Monitor for hyperglycemia. Withhold Opdivo in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue Opdivo for life-threatening (Grade 4) hyperglycemia [see Dosage and Administration].

Immune-Mediated Nephritis and Renal Dysfunction

In patients receiving Opdivo as a single agent, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients; the median time to onset was 4.6 months (range: 23 days to 12.3 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of Opdivo in 0.3% and withholding of Opdivo in 0.8% of patients. All patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 15.4 months). Complete resolution occurred in 48% of patients. No patients had recurrence of nephritis or renal dysfunction after re-initiation of Opdivo.

Management

Monitor patients for elevated serum creatinine prior to and periodically during treatment.

Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents.

Withhold Opdivo for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. Permanently discontinue Opdivo for life-threatening (Grade 4) increased serum creatinine [see Dosage and Administration].

Immune-Mediated Skin Adverse Reactions

In patients receiving Opdivo as a single agent, immune-mediated rash occurred in 9% (171/1994) of patients; the median time to onset was 2.8 months (range: <1 day to 25.8 months). Immune-mediated rash led to permanent discontinuation of Opdivo in 0.3% and withholding of Opdivo in 0.8% of patients. Approximately 16% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 days to 8.9 months) and 85% received topical corticosteroids. Complete resolution occurred in 48% of patients. Recurrence of rash occurred in 1.4% of patients who resumed Opdivo after resolution of rash.

Management

Opdivo can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold Opdivo and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue Opdivo [see Dosage and Administration].

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold Opdivo for severe (Grade 3) rash and permanently discontinue Opdivo for life-threatening (Grade 4) rash.

Immune-Mediated Encephalitis

In patients receiving Opdivo as a single agent, encephalitis occurred in 0.2% (3/1994). Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of Opdivo and administration of corticosteroids. In the other two patients, encephalitis occurred post-allogeneic HSCT [see Warnings and Precautions].

Management

Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold Opdivo in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If

other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue Opdivo for immune-mediated encephalitis [see Dosage and Administration].

Other Immune-Mediated Adverse Reactions

Opdivo can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of Opdivo therapy. For any suspected immune-mediated adverse reactions, first, exclude other causes and based on the severity of the adverse reaction, permanently discontinue or withhold Opdivo, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting Opdivo after completion of corticosteroid taper based on the severity of the event [see Dosage and Administration].

Across clinical trials of Opdivo administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in less than 1.0% of patients receiving Opdivo: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving Opdivo or Opdivo in combination with ipilimumab and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion Reactions

In patients receiving Opdivo as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a study assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received Opdivo as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of Opdivo.

Management

Opdivo can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. Discontinue Opdivo in patients with severe or life-threatening infusion reactions.

Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions [see Dosage and Administration].

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, Opdivo can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with an Opdivo-containing regimen and for at least 5 months after the last dose of Opdivo [see Use in Specific Populations in the drug packaging insert]

2.3 Rationale

ONC201 is a first-in-class small molecule with consistent antitumor activity in difficult-to-treat cancers as demonstrated using *in vitro*, *ex vivo*, and *in vivo* models. The mechanism of action of ONC201 appears to involve the activation of the ISR that causes a downstream inactivation Akt and ERK signaling as well as induction of the pro-apoptotic TRAIL pathway. The efficacy of ONC201 has been demonstrated in numerous solid and liquid tumor cell lines and patient sample that are refractory to chemotherapy and targeted therapies. ONC201 is effective in tumor cells harboring diverse mutations in genes such as p53, KRAS, Raf, EGFR and others that render resistance to chemotherapy and targeted therapies. Colon cancer has been selected for evaluation in this trial based on preclinical efficacy as well as the mechanism of action of ONC201 that involves engagement of the ISR, inactivation of Ras signaling, and induction of the TRAIL pathway that should be effective in these tumors based on preclinical and clinical evidence.

2.3.1 Rationale for combination of ONC201 with anti-PD1 Opdivo (Nivolumab)

The combination of ONC201 with anti-PD-1 therapy resulted in more potent *in vivo* tumor suppression with the combination versus anti-PD-1 therapy alone (Figure 15). (Wagner et al. J Clin Invest. 2018)

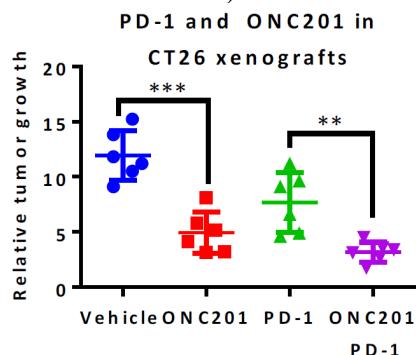


Figure 15. ONC201 in combination with anti-PD1. Relative tumor volume after 4 weeks in CT26 tumors in Balb/c mice treated with vehicle, 100 mg/kg ONC201, anti-PD-1, or ONC201 + anti-PD-1.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives – Phase Ib

3.1.1 Phase Ib: Primary Objective

- 2) Determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of ONC201 when administered orally in combination with Opdivo (Nivolumab) in patients with microsatellite stable metastatic colon cancer who progressed after at least 2 lines of therapy

3.1.2 Phase Ib: Secondary Objectives

- 1) Evaluate the overall safety profile of orally-administered ONC201 in combination with Opdivo (Nivolumab) using CTCAE version 5.0.
- 2) Evaluate the pharmacokinetic (PK) profile of orally-administered agent ONC201 in combination with Opdivo (Nivolumab)
- 3) Assess the pharmacodynamic effects of orally-administered agent ONC201
- 4) Assess preliminary efficacy of ONC201 and Opdivo

3.2 Objectives – Phase II

3.2.1 Phase II: Primary Objectives

- 1) Determine progression free survival (PFS) of orally-administered ONC201 in combination with Opdivo (Nivolumab)
- 2) Determine the response rate to ONC201 in combination with Opdivo (Nivolumab), as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1, in patients with microsatellite stable metastatic colorectal cancer

3.2.2 Phase II: Secondary Objectives

- 1) Confirm safety of phase II dose of ONC201 in combination with Opdivo (Nivolumab) using CTCAE version 5.0
- 2) Assess preliminary overall survival associated with ONC201 and Opdivo (Nivolumab) in patients with microsatellite stable metastatic colorectal cancer
- 3) Correlate clinical outcome with tumor & blood biomarkers including cancer stem cells, signaling intermediates and inhibitors, NK cells, TRAIL, granzyme, perforin, and M30.

4 STUDY DESIGN

4.1 Overview

This is a single arm Phase Ib/II, open label, safety, pharmacokinetic, pharmacodynamics and efficacy study of ONC201 in combination with Opdivo (Nivolumab) in adult patients with metastatic colorectal cancer, for whom no standard therapy is available. This study will enroll adult patients with microsatellite stable metastatic colorectal cancer who progressed after at least two lines of therapy.

4.2 Study Design

In the phase IB portion of the trial, the safety of the combination of ONC201 and nivolumab will be established in cohorts of 3-6 patients using a dose de-escalation design. Once the recommended phase 2 dose (RP2D) is determined, phase II will be initiated so a total of 34 patients will be treated at the RP2D.

Throughout the study, AEs, SAEs, laboratory values, vital signs, physical examination findings, ECOG performance status, and EKGs will be obtained to evaluate the combination treatment arms. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

Dosing phase Ib and II:

An initial dose of ONC201 will be given -7

days prior to cycle 1, day1

Cycle = 4 weeks (28 days)

- ONC201 weekly day 1
- Nivolumab 240mg IV q2 weeks day 1 and 15 over approximately 30 minutes, with ONC201

Phase IB:

Dose de-escalation, cohorts of 3-6 patients to determine RP2D

(PK, PD, tumor biopsies)



RP2D

Phase II:

28 additional patients at RP2D

(PD and tumor biopsies)

The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months, as determined by the investigator. Follow-up for all patients will be approximately 6 months.

The study is expected to be completed over an approximate 3.5-year period

Archival tissue available from prior surgery or biopsy will be collected for future testing. There is a required pre-treatment biopsy which will occur post consent and prior to run-in dose of ONC-201 (D-7). A second research biopsy will be performed post cycle 2, at approximately 8 weeks and to coincide with the first imaging. If patients progress at that time they will come off study. If

the patient has not progressed, a third research biopsy will be performed at the time of progression, if progression occurs during the study treatment or follow-up time period.

Dose-limiting toxicities (DLTs) are defined below in section 6.4.2.

Serial blood samples to measure plasma concentrations of ONC201, and potentially relevant biomarkers, will be collected at pre-specified time points as indicated in the respective Schedule of evaluations table.

4.3 Number of Patients

It is anticipated that 6 evaluable patients in the Phase IB and an additional 28 patients in Phase II will be enrolled into this study. Enrollment is estimated to occur over the course of 2 years with study completion occurring over approximately 3.5 years. Because a 3 + 3 dose de-escalation design will be used, the actual sample size will depend on the number of cohorts and the number of patients enrolled in phase Ib.

4.4 Duration of Study

A cycle is defined as q 4 weeks (28 days). Nivolumab and ONC201 will start on day 1 of each cycle (following an initial dose of ONC 201 on day -7). ONC201 will be given weekly day 1, and Nivolumab will be given q 2 weeks at a flat dose of 240mg IV over an approximate 30-minute infusion. See treatment section for details.

Dosing will continue until disease progression, unacceptable toxicity per patient or treating physician, or the patient discontinues for any other reason.

The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months, as determined by the investigator. Follow-up for all patients will be approximately 6 months.

The study is expected to be completed over an approximate 3.5-year period

When patients discontinue study treatment, they should return to the study site 30 days (+1 week) and 100 days (+1 week) after administration of the last treatment (Nivolumab or ONC201, whichever is last) to complete the safety assessment visit and procedures.

The study will be completed in approximately 3.5 years, taking into account approximately 2 years of enrollment, 12 months of treatment and approximately 6 months of follow-up, on average.

5 ELIGIBILITY CRITERIA

5.1 Inclusion

1. Patients must have a histologically/cytologically -confirmed MSS primary colorectal adenocarcinoma tumor, with confirmation of being microsatellite stable.
2. Radiographic or clinical evidence of metastatic disease that has progressed after at least 2 prior regimens. Prior bevacizumab, cetuximab, trifluridine and tipiracil, or regorafenib is allowed, prior FOLFIRI and FOLFOX treatment is required. (Treatment with a FOLFIRINOX regimen will count as 2 regimens). Prior treatment does not have to have been in the metastatic setting.
3. Patients must have measurable disease by RECIST criteria
4. All patients must have a tumor(s) located in an area that can be biopsied as confirmed by treating physician
5. All patients must submit representative tissue from their malignancy if it is confirmed there is enough tissue from prior surgery or most recent biopsy. This can consist of archival tumor samples or tissue collected at biopsy to prove recurrence. In both cases, samples should consist of a formalin-fixed paraffin embedded (FFPE) tumor tissue block or at least 20 unstained slides (charged) of 4 μ M thickness sent to the lab address outlined in section 11.1.4. Tissue located outside of Lifespan Cancer Institute hospitals must be confirmed as requested from outside organization or that it was received from outside organization prior to enrollment.
6. All previous therapies for cancer, including radiotherapy, major surgery and investigational therapies must be discontinued for \geq 14 days before the first dose of ONC201 (D-7 run in).
7. All clinically significant adverse events related to any prior therapy must have resolved to Grade \leq 1 Common Terminology Criteria for Adverse Events (CTCAE v5.0), except alopecia or parameters defined in this eligibility list.
8. Age \geq 18 years.
9. ECOG performance status \leq 2.
10. Adequate organ and marrow function as defined below:
 - a. Absolute neutrophil count \geq 1,000/mm³ without growth factor use \leq 7 days prior to treatment (this is Day -7)
 - b. Platelets \geq 75,000/mm³ without platelet transfusion \leq 7 days prior to treatment (this is Day -7)
 - c. Hemoglobin \geq 8.0 mg/dL without red blood cell transfusion \leq 7 days prior to treatment (this is Day -7)
 - d. Total serum bilirubin \leq 1.5 X upper limit of normal (ULN)

- e. AST (SGOT)/ALT (SGPT) $\leq 2 \times$ ULN; $\leq 5 \times$ ULN if liver dysfunction is felt to be secondary to tumor burden within 14 days prior to treatment (this is Day -7)
- f. Serum creatinine $\leq 1.5 \times$ ULN (OR creatinine clearance $\geq 60 \text{ mL/min}/1.73 \text{ m}^2$) within 14 days prior to treatment (this is Day -7)
- g. Serum or urine pregnancy test (for females of childbearing potential) negative ≤ 7 days of treatment (this is Day -7)

11. Ability to understand and the willingness to sign a written informed consent document and comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.
12. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception from time of consent and for the duration of study treatment through 5 months after the last dose of study treatment (ONC201 or Nivolumab, whichever is last) The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.
13. Patients must agree to the required tumor biopsies to enroll in the trial. Pre-treatment biopsies can occur any time post consent and prior to run-in ONC201 dose, a second biopsy will be required at the end of cycle 2 to assess response biomarkers, a final biopsy is included at the time of progression to assess for resistance mechanisms. Only 2 biopsies will be required for patients who initially progress at time of 2nd biopsy.

5.2 Exclusion

1. Patients with symptomatic brain metastases are excluded. Patients with asymptomatic and treated CNS metastases may participate in this trial. The patient must have completed any prior treatment for CNS metastases > 28 days prior to registration, including radiotherapy or surgery. Steroids for the treatment of brain metastasis are not permitted.
2. Patients with prior treatment with ONC201 or who have had prior therapy with nivolumab or 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 co-stimulation or immune check point pathways will be excluded
3. Active inflammatory gastrointestinal disease such as severe chronic diarrhea (unless related to underlying malignancy), gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study registration. Gastroesophageal reflux disease under controlled treatment with proton pump inhibitors is allowed.
4. Pregnant or breast feeding.
5. Current active treatment in another clinical study (treatment trial) within 14 days of D-7.

6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics, hepatitis, active rheumatologic or collagen vascular disease, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

NOTE: Participants with active or a history of Hepatitis B or C infection as follows:

Active hepatitis B (positive hepatitis B surface antigen [HBsAg] or hepatitis C virus (HCV) (positive HCV RNA) are not eligible to participate.

HBV carriers or those participants requiring antiviral therapy are not eligible to participate.

Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA. If PCR is positive, they are not eligible to participate.

Past HBV infection or resolved HBV infection are may be eligible on this trial provided the following criteria are met prior to randomization: Positive for hepatitis B core antibody (HBcAb), the absence of hepatitis B surface antigen (HBsAg), and no detectable HBV DNA in serum.

7. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. (testing is not required for eligibility).
8. Any of the following in the previous 3 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism as defined by treating physician.
9. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.
10. Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
11. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day 1 of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease
12. Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer are excluded if there is any evidence of other malignancy being present within the last three years (2 years for invasive breast cancer). However, patients with a malignancy that is non-likely to require treatment, as per the treating physician, in the next

2 years, such as a completely resected, early stage breast cancer, or other malignancies treated with curative intent are eligible. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

13. Prior treatment with immunotherapy for any cancer, including immune checkpoint inhibitors or anti-CTLA4 agents
14. Participants who have received a live / attenuated vaccine within 30 days of first treatment.

5.3 Contraception

During the study, fertile female patients must take precautions to prevent pregnancy since the effects of the study medication on the fetus are unknown. Male patients with partners of childbearing potential must take precautions to prevent pregnancy of the partner since the effects of this drug on sperm are unknown. These restrictions should remain in force for 5 months from the last dose of investigational agent (Nivolumab or ONC201) for WOCBP and for 7 months from the last dose of investigational agent (Nivolumab or ONC201). Drug interaction studies with oral contraceptives have not been performed, so barrier methods of contraception or abstinence should be considered. The definition of effective contraception should be in agreement with local regulation and based on the judgment of the principal investigator or a designated associate. A suggested definition of adequate contraception is the use of double barrier contraception (e.g., condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device).

5.4 Inclusion of Women and Minorities

Women and Men of all races and ethnic groups are eligible for this trial.

5.5 Patient Registration

Details of patient's study participation should be documented in clinic/file notes. This project will leverage the Lifespan REDCap instance for making electronic health data accessible for research purposes. REDCap was developed by Vanderbilt University with collaboration from a consortium of institutional partners as a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. The REDCap platform is a secure, web-based application flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data, and enforces real time validation rules (with automated data type and range checks) at the time of entry. This platform provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, and real-time data monitoring/querying of participant records. REDCap has multiple data export options to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The investigator will electronically sign the REDCap case reports prior to DSMB review and at the end of follow-up, to indicate that, to his/her knowledge, they are complete and accurate.

All support data must be sent in for registration only. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must electronically sign the off-study form. Sites are to be sure that elements to support

all inclusion and exclusion criteria are submitted and that all assessments from the study procedures calendar (section 8) are submitted for registration.

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, and the signed Patient Consent Form must be emailed to the BrUOG Central Office to allow for registration and prior to patient treatment. Registrations should be planned such that the BrUOG office has a full 2 business days to review all registration packets, prior to the scheduled date of treatment (D-7).

6 STUDY TREATMENTS

6.1 Biopsy & Tissue:

There are 3 specimens anticipated for collection, a pre-BrUOG 379 treatment biopsy and a mid-treatment biopsy- both of which are required. If the patient does not progress at time of 2nd biopsy, there is a required 3rd biopsy to occur at time of progression (if patient progresses during treatment/follow-up time period)

All collected specimens will be stored in the laboratory of Dr. Wafik El-Deiry for correlative testing for future exploratory analyses to assess biomarkers associated with treatment using nivolumab and ONC201 in metastatic colon cancer.

Archival Tissue: All patients must submit representative tissue from their malignancy if it is confirmed there is enough tissue from prior surgery or most recent biopsy. This can consist of archival tumor samples or tissue collected at biopsy to prove recurrence. In both cases, samples should consist of a formalin-fixed paraffin embedded (FFPE) tumor tissue block or at least 20 unstained slides (charged) of 4 uM thickness sent to the lab address located in section 11.1.4. Tissue located outside of Lifespan Cancer Institute hospitals must be confirmed as requested prior to enrollment.

6.2 Treatment Regimen

This is a single arm study with no randomization. All enrolled patients will receive the study drugs.

All patients will receive a dose of ONC201 prior to starting cycle 1, 7 days (-7 days) prior to cycle 1 day 1 and prior to beginning the combination therapy.

Each cycle is 4 weeks long (28 days). Nivolumab: For cycle 1 day 1 in phase Ib and phase II, only a +2 day window is allowed.

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The treatment dose of nivolumab is 240 mg. No dose reductions or escalations will be allowed for nivolumab. Dosing delays and modifications are described in Section 6.3-6.5 (DLT, Dosing Delays/Dose Modifications).

The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months, as determined by the investigator. Follow-up for all patients will be approximately 6 months.

The study is expected to be completed over an approximate 3.5-year period

If nivolumab is permanently discontinued due to toxicity, and the patient has had stable or responding disease, then ONC201 may be resumed when toxicity resolves to grade ≤ 1 . If the patient develops recurrent grade ≥ 3 toxicity while on single agent ONC201 after stopping nivolumab then ONC201 will be permanently stopped and the patient removed from protocol treatment.

(The rationale for continuing single agent ONC201 is to gather additional information of the efficacy of ONC201 in colon cancer. As described in section 2.1.2.1 ONC201 has activity in colon cancer cell lines. As described in section 2.2.1, in the phase I study, one patient with metastatic colon cancer that had progressed after multiple lines of standard therapy, had prolonged stable disease with ONC201. Since preliminary studies of ONC201 have demonstrated a promising toxicity profile, it may be helpful to continue ONC201 in stable/responding patients if nivolumab is stopped for immune toxicities.)

If ONC201 is permanently discontinued due to toxicity then nivolumab will be stopped and patients will be removed from study treatment.

When Nivolumab and ONC201 are both due, if administration of nivolumab is delayed based on section 6.6, ONC201 may be given alone, as long as the patient meets criteria for ONC201 dosing. If it is day 1 of a cycle, please also refer to section 6.3.

Nivolumab Description

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Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length=4 weeks
Nivolumab	No premedication or hydration necessary. Subjects should be carefully monitored, as per institutional policy, for infusion reactions during nivolumab administration.	240 mg	IV over approximately 30 minutes	Day 1	Dosing: Q 14 days (2 weeks +/- 2 days) For cycle 1 day 1 a + 2 day window only is allowed

There will be no dose reductions for Nivolumab. All patients should continue to meet treatment parameters required at eligibility, unless as otherwise specified below.

Nivolumab is to be administered as an approximate 30-minute IV infusion. For details on prepared drug storage, preparation, and administration, please refer to the Nivolumab Investigator Brochure (IB). The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at 240 mg. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

ONC201: dose de-escalation will proceed according to a standard 3 + 3 design. Dosing is to be given day 1 of each week and is to occur with Nivolumab dosing when each drug is to be given on the same day. There is a +/- 2-day window.

On days when ONC201 and nivolumab are administered on the same day, ONC201 should be administered within (\leq) 30 minutes **after** completion of nivolumab

If drug cannot be given within the required time-frame, utilizing the window, then the dose is considered missed and is not made up.

All patients will ingest ONC201 capsules in front of research clinical staff during cycle 1.

ONC201 will be taken in front of research staff in cycle 1. Patients are to bring ONC201 drug into clinic day -7, day 1, day 8, day 15, day 22.

Example Phase Ib:

Run-in Day -7: January 7, 2019 ONC201 dose 1

Cycle 1 day 1: January 14, 2019 Nivolumab and ONC201 dose 2 (+ 2-day window allowed, both drugs to be given together)

Cycle 1 week 2: January 21, 2019 ONC201 dose 3 (+/- 2-day window allowed)

Cycle 1 week 3: January 28, 2019 Nivolumab and ONC201 dose 4 (+/- 2-day window allowed, both drugs to be given together)

Cycle 1 week 4: February 4, 2019 ONC201 dose 5 (+/- 2-day window allowed)

End of cycle 1

Dose de-escalation schedule for phase 1b trial ONC201:

Doses in table are exact flat doses. Doses are not adjusted for body weight.

Dose Level	Dose of ONC201* (mg) every week, day 1 (to occur with Nivolumab dosing when both drugs are due)
Level 1 (starting dose level)	625mg
Level 2	500mg
Level 3	375mg

The starting dose schedule of ONC201 will be 625 mg administered once every 1 week, which has been established to be safe in the first-in-human trial in advanced solid tumors (Stein et al, JCO, under review).

Dose limiting Toxicities (DLTs):

DLTs will be assessed in the phase Ib portion of the trial. DLTs will be collected during the run-in (dose 1 of ONC201), cycle 1 and prior to dosing cycle 2 day 1. All patients in a cohort must be assessed for DLTs through pre-dosing cycle 2 day 1 prior to the next cohort being opened.

6.3 New cycle requirements (cycle 2-on) (Refer to sections 6.4, 6.5 and 6.6 before dosing)

A new course of treatment (cycle) with ONC201 and Nivolumab should not begin until the

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following criteria are met.

- Platelets $\geq 75000/\text{mcl}$
- Granulocytes (ANC) $\geq 1000/\text{mcl}$
- Recovery from other clinically significant, treatment related non-hematologic toxicities to \leq Grade 2

When Nivolumab and ONC201 are both due, if a patient is unable to receive Nivolumab based on section 6.6, ONC201 may be given alone, as long as the patient meets criteria for ONC201 dosing. If it is day 1 of a cycle, please also refer to section 6.3.

6.4 Determination of the MTD and RP2D

Dose limiting Toxicities (DLTs):

DLTs will be assessed in the phase Ib portion of the trial. DLTs will be collected during the run-in (dose 1 of ONC201), cycle 1 and prior to dosing cycle 2 day 1. All patients in a cohort must be assessed for DLTs through pre-dosing cycle 2 day 1 prior to the next cohort being opened.

Dose Definitions (MAD, MTD, RP2D)

The maximally tolerated dose (MTD) is defined as the dose frequency schedule above which the absolute observed DLT rate is $> 25\%$. The MTD is equivalent to the anticipated recommended phase 2 dose (RP2D).

However, the final RP2D may also be influenced by pharmacokinetic information, additional emerging toxicity data, pharmacodynamic data, or practical dosing (capsule load) information. The RP2D will never exceed the MTD.

The MAD, or maximally administered dose, is estimated to be 625 mg (5 capsules) given weekly, beginning day -7 (phase Ib) and day 1 (phase II).

6.4.1 Dose Limiting Toxicity (DLT) definition

Toxicity will be evaluated according to the NCI CTCAE, version 5.0.

DLTs will be collected during the run-in (dose 1 of ONC201), cycle 1 and prior to dosing cycle 2 day 1. All patients in a cohort must be assessed for DLTs through pre-dosing cycle 2 day 1 prior to the next cohort being opened.

If, however a patient experiences one of the below toxicities after cycle 2 or in the phase II portion it will not be considered a DLT, however: hold treatment (both drugs), once the toxicity reduces to a grade 1 or less, dose reduce (ONC201) and resume treatment, even though it will no longer be defined as a DLT.

A DLT will be defined as any of the following AEs that are attributed to the study drugs (Nivolumab or ONC201):

If a patient experiences a DLT, hold treatment (both drugs) until the adverse event reduces to a grade 1 or less and resume ONC201 at 1 dose level reduction. Nivolumab is not to be dose reduced.

If nivolumab is permanently discontinued due to toxicity, and the patient has had stable or responding disease, then ONC201 may be resumed when toxicity resolves to grade ≤ 1 . If the patient develops recurrent grade ≥ 3 toxicity while on single agent ONC201 after stopping nivolumab then ONC201 will be permanently stopped and the patient removed from protocol treatment.

6.4.2 DLT definitions phase Ib:

(Run-in Day -7, cycle 1 and pre-cycle 2), Events occurring in cycles 2-12+ in phase Ib or in phase II will be not be considered a DLT however both treatments must be held and once toxicity reduces to grade 1 or less, dose reduce ONC201:

Hematologic:

- Grade 4 neutropenia that persists for >7 consecutive days
- Febrile neutropenia (defined as neutropenia \geq Grade 3 and a body temperature 38.5°C)
- Grade ≥ 3 neutropenic infection
- Grade 4 thrombocytopenia (platelets $<25,000$ cells/mm 3) or Grade ≥ 3 thrombocytopenia with bleeding

Non-hematologic:

- Any other treatment related, clinically significant Grade ≥ 3 toxicity not classified under CTCAE blood or bone marrow with the exception of grade 3 nausea, vomiting, or diarrhea in patients who have received optimal treatment with antiemetics or anti-diarrheals and who do not downgrade to a grade 1 within 72 hours; Grade 4 (life threatening) diarrhea or vomiting will be considered DLTs, irrespective of the duration of the event. alopecia is not a DLT
- Delay of > 2 weeks secondary to a treatment related AE that is deemed possibly or definitely related to either drug
- Failure to receive at least 80% of the planned dose on ONC201 due to treatment related AEs (ONC201) in cycle 1 (5 doses ONC201 with run-in).

Although toxicities may be observed at any point during treatment, only those occurring during the defined DLT observation window of treatment that are considered DLTs will guide dose escalation decisions, expansion of a dose level, or evaluation of intermediate dose levels.

Patients will be monitored through all cycles of therapy for treatment-related toxicities, and all toxicities, including those occurring in beyond the DLT observation window, will be documented.

6.4.3 Dose de-escalation:

Dose de-escalation will proceed by a 3+3 design. Cohorts will be de-escalated in successive cohorts of 3 to 6 patients.

Patients failing to complete the first 4 weeks of treatment for reasons other than toxicity (e.g., lost to follow up, patient withdrawal, progression) will be replaced for the purpose of meeting the primary objective of this study.

Starting with the treatment of 3 patients at the planned dose cohorts described previously, the administration of ONC201 will follow traditional 3 + 3 dose de-escalation rules summarized below:

1. Dose level 1: Enroll 3 patients.
2. If 0 of 3 patients experience a DLT, 3 additional patients will be enrolled at that same dose cohort to confirm safety. If < 1 (no patients) of these 6 subjects encountered a DLT, then this dose level will be declared to be the MTD. This dose level will be expanded to treat 34 patients in phase II.
3. If 1 of 3 patients experience a DLT, 3 additional patients will be enrolled at that same dose cohort. If 2 or more of the 3-6 subjects within a cohort encounter a DLT, then the MTD has been exceeded and de-escalation will proceed to the next dose level (dose level 2 etc.). Only 2 dose reductions of ONC201 will be allowed.

6.5 ONC 201 Dose Delays/Holds Phase II: Dose Delays, Reductions and Interruptions for toxicities that are deemed related (some causality) to ONC201 During the Phase II Portion of the Study:

Adverse Event	Dose Adjustment
Grade 1 and 2	<ul style="list-style-type: none"> • No change in dose
Grade 3	<p>Hold ONC201</p> <p>Resumption of ONC201 may continue as outlined below:</p> <ul style="list-style-type: none"> • First occurrence: Hold ONC201 until \leq Grade 1. Resume ONC201 at one dose frequency cohort lower • Second occurrence: Hold ONC201 until \leq Grade 1. Resume ONC201 at one dose frequency cohort lower with \sim half the number of capsules administered followed by the administration of the other half of the capsules 6-12 hours later • Third occurrence: Off protocol therapy
Grade 4	<ul style="list-style-type: none"> • Off protocol therapy

If, however a patient experiences a “DLT toxicity” after cycle 2 or in the phase II portion it will not be considered a DLT, however: hold treatment (both drugs), once the toxicity reduces to a grade 1 or less, dose reduce (ONC201) and resume treatment, even though it will no longer be defined as a DLT.

On a day when Nivolumab and ONC201 are both due, if a patient is unable to receive Nivolumab based on section 6.6, ONC201 may be given alone, as long as the patient meets criteria for ONC201 dosing. If it is day 1 of a cycle, please also refer to section 6.3.

6.6 Dose delays for Nivolumab Phase Ib and Phase II:

Non-Immune mediated: All clinically significant (grade 3 or higher) hematologic and non-hematologic toxicities felt to have some causality to nivolumab must resolve to \leq grade 2 (excluding weight loss, weight gain, and alopecia) or to baseline prior to a patient receiving a subsequent dose (of Nivolumab). Any dose of nivolumab not administered will be skipped and not made up if outside of the \pm 2-day window.

Immune mediated: Adverse events (both serious and non-serious) associated with nivolumab may represent immunologic etiology.

Nivolumab must be held for suspected immune-mediated toxicities or severe/life-threatening AEs of particular interest as outlined in section below and immune-related toxicities in Appendix D. Please review both Sections (6.6 (below) and Appendix D) prior to infusion of nivolumab in any patient in whom immune-mediated toxicity is suspected.

If the investigator is unsure if a particular toxicity at least possibly represents an immune mediated toxicity to nivolumab, the treating physician should follow section 6.5 (this section) and appendix D and treat as immune mediated, until it is confirmed as not being immune mediated. Consultation with BrUOG is suggested in such situations. BrUOG will share information about the situation with the BrUOG Reviewer and provide the site guidance, as available.

Except on day 1 of a cycle, when Nivolumab and ONC201 are both due, if a patient is unable to receive Nivolumab based on section 6.6, ONC201 may be given alone, as long as the patient meets criteria for ONC201 dosing. If it is day 1 of a cycle, please also refer to section 6.3.

Prior to treatment of either arm or either drug, the following criteria must be met as they pertain to related (to either or both drugs) immune mediated events:

- ANC \leq grade 3 (must be \geq 500).
 - Febrile neutropenia or neutropenia $<$ 500 cells/mm³ (grade 4).
 - If Grade 4 neutropenia persists for greater than one week, the patient is required to come off study.
- Hyperthyroidism or Hypothyroidism: grade will be based on patient symptoms, not solely on whether suppression or supplementation is indicated.
 - Grade 1 asymptomatic
 - Grade 2 symptomatic, limiting instrumental ADLs
 - Grade 3 severely symptomatic, limiting self-care ADLs, hospitalization indicated
 - Grade 4 Life threatening consequences, intervention indicated. Requires patient to come off study
 - Grade 5 death

Patients meeting criteria of Grade 2 or greater must resolve to Grade 1, be on stable hormone therapy, and complete steroid taper (if indicated). Of note, a patient who meets grade 1 criteria, but who is on a stable dose of hormone therapy, is allowed to receive treatment on study.

- Diarrhea and enterocolitis $<$ grade 2
 - Grade 2: delay until \leq grade 1 and resume at discretion of treating MD
 - Grade 3 or 4: Patient off study
- Transaminase and Bilirubin $<$ grade 2
 - Grade 2: Hold until \leq grade 1 and increase monitoring as per table

- Grade 3 or 4: remove from study, see appendix D for details on grade 3
- Lipase and amylase < grade 4
 - Grade 2 with findings of pancreatitis: hold until resolved
 - Grade 3 or 4: Lipase or amylase elevations only patient may continue on study with monitoring
 - Grade 3 or 4 pancreatitis or worsening DM: remove from study
- Neurological events (inclusive of neuropathy if not present at baseline) < grade 2
 - Grade 2: Hold until \leq grade 1. If steroids needed, remove from study
 - Grade 3 or 4: remove from study
- Pneumonitis < grade 1
 - Grade 1: Consider delay of treatment, but may proceed with treatment at the discretion of the treating physician.
 - Grade 2: Delay until < grade 1. Consider steroids (see Appendix D, Pulmonary AE Management Algorithm). If not improving after 2 weeks or worsening symptoms, treat as Grade 3 or 4. If improving, taper steroids over at least 1 month once symptoms return to or near baseline and resume protocol treatment.
 - Grade 3 or 4: remove from study
- Creatinine < grade 2
 - Grade 2 and 3: Hold until \leq grade 1. Consider steroid treatment (see Appendix D, Renal AE Management Guideline).
 - Grade 2 or 3 for > 7 days: treat as a grade 4
 - Grade 4: remove from study
- Skin rash (all types) and oral lesions \leq grade 2
 - Grade 3: Hold until \leq grade 1
 - Grade 4: remove from study
- Fatigue \leq grade 2
 - Grade 3: Hold until < grade 2 if within 7 days. If persists >7 days, remove from study.
 - Grade 4: remove from study
- Fever < grade 2
 - Grade 2, 3: hold until \leq grade 1
 - Grade 4: remove from study

6.6.1 Nivolumab Removal from study:

Patients must discontinue nivolumab permanently for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period
OR requires systemic treatment

- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding
- Any treatment delay resulting in no nivolumab dosing for > 6 weeks.
- Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, hypophysitis.
- \geq Grade 3 or 4 hepatic AEs * see appendix D for details
- \geq Grade 4 skin toxicity (per Appendix D can delay or discontinue for grade 3. Must come off, as per this bullet for grade 4 skin)
- ALL OTHER treatment related grade 3/4 treatment related events with the following exceptions:
 - Grade 4 neutropenia \leq 7 days;
 - Grade 4 lymphopenia or leukopenia;
 - isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset;
 - Grade 3 hepatic AEs that return to Grade 2 or less within 5 days; of note, this overrides Appendix D
 - Skin toxicity \leq grade 3 that improves with steroid therapy. NOTE: Any rash consistent with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis requires permanent discontinuation of nivolumab.
 - Grade 3 renal toxicity (as per Appendix D)

6.6.2 Treatment of Nivolumab Infusion Reactions:

Nivolumab is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE 5.0 guidelines.

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

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

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent)

and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

Immediately discontinue infusion. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

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

6.6.3 Immune-Related Adverse Events (irAEs) General Definition, Monitoring, and Management

For the purposes of this protocol, an immune-related adverse reaction irAE is defined as an adverse reaction of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an event an irAEs. Serologic, immunologic, and histologic (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Suspected immune-related adverse reactions must be documented on an AE or SAE form.

Overall, immune-related AEs commonly start within 3 to 10 weeks from initiation of therapy and are in most cases successfully managed by delaying doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned below. Immune-related AEs generally resolved within days to weeks in the majority of subjects.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic immune-mediated adverse reactions (e.g., systemic lupus erythematosus-like diseases) or organ specific immune-mediated adverse reaction (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an immune-mediated adverse reaction is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on nivolumab activity. If utilized, corticosteroid therapy should be individualized for each patient. For example, prior experience suggests that colitis manifested as \geq grade 3 diarrhea requires corticosteroid treatment. If an irAE is documented, in general, delay protocol therapy and initiate corticosteroids earlier to obtain resolution with the possibility for resuming protocol therapy rather than waiting for higher grade events.

Investigators should as a rule evaluate suspected adverse effects early, and with any suspicion, erring on the side of caution by withholding drug and instituting appropriate treatment as indicated in the management tables and following event specific guidelines.

6.6.4 Immune-mediated Endocrinopathy

Agents such as nivolumab can cause inflammation of endocrine organs including thyroid (Hashimoto's thyroiditis with positive antibodies) and adrenal glands, hypophysitis, hypopituitarism, and resulting thyroid and adrenal insufficiency, low ADH, prolactin, FSH, LH. Hyperthyroid with Graves' disease and positive antibody has been reported. Patients may present with subtle and nonspecific symptoms. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, and

electrolyte disturbances including hyponatremia and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the subjects symptomatically improved with hormone replacement therapy.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Headache is often the first symptoms of hypophysitis. Patients may present with fatigue, headache, mental status changes, loss of libido, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathy should be considered immune-mediated and drug withheld pending evaluation. Patients may demonstrate both central (hypophysitis) and peripheral adrenal and thyroid insufficiency. Evaluation of hypophysitis should include pituitary MRI.

In this study, TSH will be performed at baseline prior to initial treatment. TSH levels, clinical chemistries and clinical assessment is to be performed using the schedule below, with further evaluation as clinically indicated. Monitoring TSH may allow early detection of pituitary dysfunction and hypophysitis. Clinical monitoring of symptoms may be equally or more sensitive as an initial presentation. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Please see Appendix D (Endocrinopathy Management Algorithm) for guidelines on managing adverse events.

6.6.5 Immune-mediated enterocolitis

The clinical presentation of GI immune-related AEs included diarrhea, increase in the frequency of bowel movements, abdominal pain, or hematochezia, with or without fever. However, inflammation may occur in any part of the GI tract including esophagitis and gastritis. Fatalities due to GI perforation have been reported in clinical trials of Ipilimumab in particular. Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea, or GI perforation. Diarrhea or colitis occurring after initiation of nivolumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation to establish etiology and for persistent or severe symptoms. *C. difficile* toxin has been detected in several patients with colitis and may be an independent entity or may co-exist with ipilimumab induced inflammatory colitis.

Permanently discontinue nivolumab in patients with severe enterocolitis (see table below), and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of methylprednisolone IV or IV equivalent. Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering of ipilimumab has resulted in recurrence or worsening symptoms of enterocolitis in some patients receiving ipilimumab. Patients have been treated with anti-TNF agents (e.g., infliximab) for persistent colitis not responding to steroids.

Please note autoimmune pancreatitis may cause abdominal pain and should be included in all evaluations. Enteritis may occur occasionally with other autoimmune events including hepatitis, pancreatitis, and endocrine insufficiency, which should be evaluated as clinically indicated.

Please refer to the GI Adverse Event Management Algorithm in Appendix D for guidance on toxicity management.

6.6.6 Immune-mediated hepatitis and pancreatitis

Hepatic immune-related AEs are mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. **Serum transaminase, bilirubin and lipase levels must be evaluated before each protocol directed therapy infusion as early laboratory changes may be indicative of emerging immune-related hepatitis/ pancreatitis and elevations in liver function tests (LFTs) may develop in the absence of clinical symptoms.** Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or other medications, and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity have shown evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

Monitor levels of hepatic transaminases, bilirubin, and lipase and assess patients for signs and symptoms of hepatotoxicity/pancreatitis before each protocol directed therapy infusion. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution. Please see the Hepatic Adverse Management Guideline in Appendix D for further guidance.

The management of pancreatitis is given below.

Pancreatitis Amylase/Lipase	Management/Next Dose for Nivolumab
Grade 1	Continue protocol therapy and monitor. Asymptomatic lipase/amylase elevation, continue protocol therapy and monitor patient clinically.
Grade 2	For amylase/lipase elevations only, continue protocol therapy and monitor patient clinically. For radiographic findings consistent with pancreatitis, hold protocol therapy until resolved.

Pancreatitis Amylase/Lipase	Management/Next Dose for Nivolumab
Grade 3	Discontinue protocol therapy for development of Grade 3 pancreatitis or for new or worsening DM. Evaluate for co-existing hepatitis/cholecystitis. For amylase/lipase elevations only, continue protocol therapy and monitor patient clinically.
Grade 4	Discontinue protocol therapy for development of Grade 4 pancreatitis or for new or worsening DM. For amylase/lipase elevations only, continue protocol therapy and monitor patient clinically. Consider imaging if no improvement or worsening.

Pneumonitis

Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids, see Opdivo package insert for further information. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Consider recommending seasonal influenza killed vaccine for all patients.

Please refer to Appendix D for management of pulmonary adverse events.

6.6.7 Renal Adverse Events

Please refer to Appendix D for management of renal adverse events.

6.6.8 Immune-mediated dermatitis

Skin immune-related AEs presented mostly frequently as a rash and/or pruritus. Some subjects reported vitiligo associated with nivolumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab. Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. For further information, refer to Appendix D for management of skin adverse events.

6.6.9 Fatigue

Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, hepatic, and/or muscle (CPK) inflammation.

FATIGUE	Management/Next Dose for Nivolumab
Grade 1	Continue protocol therapy
Grade 2	Continue protocol therapy
Grade 3	Hold protocol therapy. Resume protocol therapy if \leq Grade 2 within 7 days.
Grade 4	Discontinue protocol therapy

6.6.10 Fever

Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.

Fever	Management/Next Dose for Nivolumab
Grade 2	Hold protocol therapy until $<$ grade 1. Then resume protocol therapy
Grade 3	Hold protocol therapy until $<$ grade 1. Then resume protocol therapy
Grade 4	Discontinue protocol therapy

6.6.11 Other immune-mediated AEs (eg, ocular, joint, myocardial, pericardial) – See Appendix

Other immune-mediated AEs not addressed have been observed with these agents. Permanently discontinue nivolumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent for severe immune-mediated adverse reactions. Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis.

ALL OTHER EVENTS	Management/Next Dose for Nivolumab
\leq Grade 1	Continue protocol therapy at investigator discretion.
Grade 2	Consider corticosteroids as clinically indicated. Hold until \leq grade 1 OR baseline, then resume protocol therapy.
Grade 3	Discontinue protocol therapy
Grade 4	Discontinue protocol therapy

Any patient started on corticosteroids initially who is subsequently determined not to require steroids treatment for an autoimmune adverse event may resume therapy at the discretion of the investigator. In such a case, steroids should be slowly tapered.

6.7 Permitted and Prohibited concomitant medications and interventions

All supportive therapy for optimal medical care will be given during the study period at the

discretion of the attending physician(s) within the parameters of the protocol and documented source documents as concomitant medication.

6.7.1 Permitted Supportive/Ancillary Care and Concomitant Medications

- Analgesics
- Antibiotics
- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antihistamines
- Corticosteroids +/- mineralocorticoid component
- Hydration
- Immunosuppressive agents – other
- Infliximab
- Mycophenolate mofetil
- Nutritional supplementation
- Interventional use of growth factors is allowed if deemed necessary by the Investigator but only to treat grade 4 neutropenia or febrile neutropenia. Erythropoietin use is discouraged in accordance with ASCO guidelines.

6.7.2 Prohibited therapies

- Chronic systemic corticosteroids or other immunosuppressive agents for conditions other than for hypersensitivity or immune adverse effects associated with nivolumab as specified in the protocol.
Patients in this study may use standard vaccines. Where possible, routine vaccination for influenza, pneumococcal pneumonia should be given prior to the start of therapy but may be administered during treatment when clinically indicated. Vaccination should be given when there is enough separation to distinguish any vaccine reactions from drug toxicity. NOTE: There is no experience using live attenuated vaccination during nivolumab therapy, so live vaccine should be used cautiously during treatment.
- Concomitant systemic or local anti-cancer medications or treatments are prohibited.
- Erythropoietin is discouraged in accordance with FDA guidelines.
- Treatment with other anticancer or experimental drugs is not permitted for patients treated on this protocol.
- All palliative care necessary for optimal care of the patient should be provided. Palliative radiation is not allowed on study. If a patient requires palliative radiation they should be removed from the study.

- Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.

7 Drug Supply ONC201

7.1.1 Formulation, packaging and storage

The study drug ONC201 is provided as 125 mg free base (approximately 150 mg of dihydrochloride), that may include microcrystalline cellulose, sodium starch glycolate, and/or magnesium stearate as excipients, filled into hydroxypropyl methylcellulose (HPMC) capsule shells.

The ONC201 drug product capsules are intended for oral administration. The product is stored in a multi-dose container. The capsules are packaged in high-density polyethylene (HDPE) white opaque bottles, closed with an induction seal and capped with a white ribbed SecuRx® polypropylene (PPE) cap. The capsules are to be stored in the original closed container at room temperature (15 to 30°C).

As of February 2019, ONC201 is produced with 10 capsules per bottle. This may vary in the future, however the number of capsules will be documented on the product label, per package.

The study drug bottle label bears the following information:

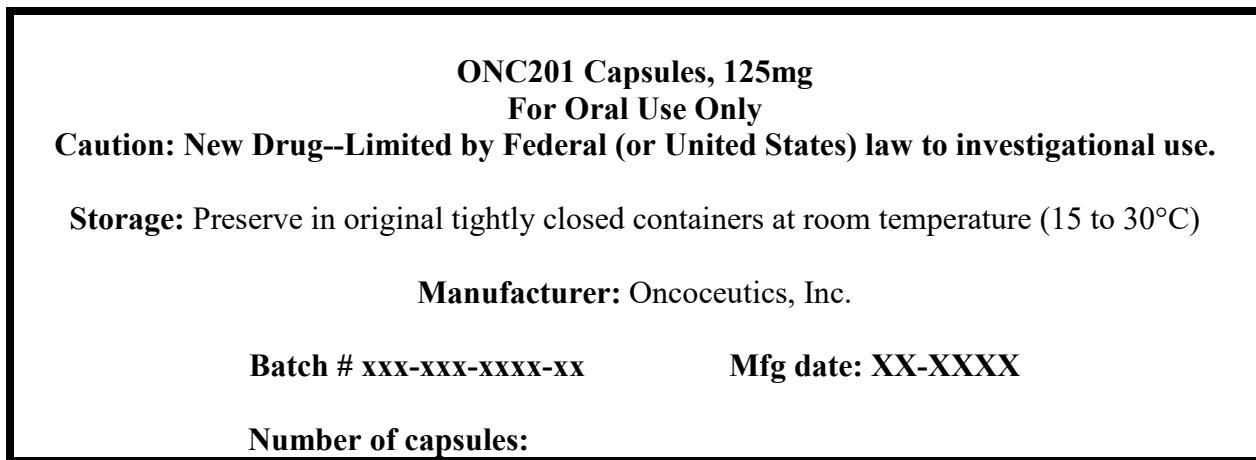


Figure 18: Investigational drug label

7.1.2 Drug accountability

Upon receipt at the investigative site, study drug product must be stored at room temperature in the original packaging. The drug should be protected from light and excessive humidity in a monitored, locked, secure area with limited access. Storage area temperature conditions must be monitored and recorded daily.

All temperature excursions will be reported to the Oncoceutics for assessment and authorization for continued use. BrUOG is required to be cc'd on this communication (BrUOG@brown.edu). Oncoceutics contact: Rohinton.tarapore@oncoceutics.com

Study site staff must instruct patients on how to store and administer oral study drug agents that are dispensed for at-home administration, except in cycle 1.

Accountability for study drug product is the responsibility of the investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (patient-by-patient accounting), and accounts of any study treatment accidentally or deliberately destroyed. A written explanation must be provided for any discrepancies.

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

Patients are to be instructed on proper accountability of the take-home study drugs and will be instructed to return any unused drug in the original packaging along with their completed diary cards at the appropriate clinic visits.

The investigator must destroy or return all unused drug product provided, once approved to do so by BrUOG, who will obtain confirmation from Oncoceutics.

7.1.3 Destruction and Return

At the end of the study, unused supplies of ONC201 will be destroyed according to institutional policies once BrUOG confirms and approves destruction. BrUOG will obtain approval to destroy from Oncoceutics. Destruction will be documented in the Drug Accountability Record Form and the form will be routed to BrUOG. Each participating hospital and pharmacy must submit, up front and throughout the trial, the most up to date drug destruction policy, to BrUOG.

Drug that is used (partially used vial for examples), can be destroyed in real-time as per the pharmacy destruction policy and do not need to be tracked on the accountability log.

Expired drug: Contact BrUOG to provide the number of expired vials/bottles and the current

accountability logs. BrUOG will obtain approval to destroy drug and will communicate approval to the pharmacy. BrUOG will then require submission of the drug accountability log, documenting the drug destruction of expired material.

7.1.4 Administration

All patients will ingest capsules in front of research clinical staff during cycle 1. The capsules are not to be chewed or broken but need to be swallowed whole. ONC201 should be taken with a glass of water on an empty stomach, with no food for 2 hours prior to dosing or 2 hours following dosing. The capsules should be taken at approximately the same day each week, at the same time on that day.

7.1.5 Drug ordering

Initial:

- Following submission and approval of the required regulatory documents, BrUOG will share all approval documented with Oncoceutics and once confirmed by Oncoceutics and BrUOG, and post the SIV, BrUOG will activate the participating hospital, which will allow for initial drug request.

All drug orders:

- There is no drug order form for this trial, the drug request must be sent to the following email addresses, with the following information. Please allow 7-10 days for delivery.
 - Name of the PI, BrUOG 379, number of active patients, number of capsules dispensed per week, and delivery address.
- It is required that the pharmacist confirm receipt of the requested drug shipment to the email addresses as well.
- The drug request email must be printed and saved in the BrUOG 379 pharmacy study binder, along with the shipment/packaging slip and confirmation of receipt email.
- All drug orders must be emailed to:
 - rohinton.tarapore@oncoceutics.com
 - cc to BrUOG@brown.edu

7.2 ONC201 Dose Modifications for phase II (see section 6.5)

For treatment-emergent AEs, the dose-frequency of ONC201 will generally be held until resolution or lowered. However, preclinical studies suggest that adverse events can be mitigated by dose fractionation to lower C_{max} . Thus grade 3 AEs (second occurrence) may be reduced or eliminated on subsequent cycle by dose fractionation. Six-hour separation of fractionated doses is selected based on the anticipated half-life of ONC201 in man and may be adjusted based on clinical data. In situations where this occurs during cycle 1, site personnel will be instructed in regards to pharmacokinetic blood draws, which will be modified.

The protocol intends to dose patients with the full intended dose at one time, given the preclinical safety data and pharmacodynamic data which supports such dosing. However, preclinical data suggests that dose fractionation could potentially mitigate treatment-emergent adverse events, which may be C_{max} driven. Therefore, if a pattern of adverse events emerge during the conduct of the study and a mitigation strategy is felt to be warranted, the patient dose will be fractionated. Should this occur, a note-to-file will support the change in dosing and the protocol will reflect the updated dosing if an amendment is published. The total dose will be split into two doses and administered 6 hours apart from each other. The smaller amount of capsules will be given first, followed by the larger amount of capsules 6 hours later (e.g.: 625 mg dose level will be given as 250 mg in the AM, followed by 375 mg 6 hours later). This strategy may be employed on an individual patient, if dose-modification due to a treatment-related adverse event does not adequately mitigate the AE after a dose delay or dose reduction, as detailed in Section 5.5 (Table 4).

7.3 Concomitant Medications ONC201

7.3.1 Drug Interactions

No formal metabolic or drug-drug interactions with ONC201 or any metabolites have been performed. These studies will be performed later in the development of this agent. A literature search revealed that ONC201 was inactive in a CYP450 screen. Strong inducers and inhibitors of the cytochrome P450 system should be used with caution.

7.4 Nivolumab Drug Supply:

7.4.1 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with Nivolumab administered in this study can be found in Section 6.5

7.4.2 Description

Nivolumab is an anti-PD-1Mab with a molecular weight of 146,221 daltons. Nivolumab targets the programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few particulates

may be present. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), pH 6.0.

7.4.3 Form

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), pH 6.0.

Nivolumab is supplied by Bristol-Myers Squibb as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL type I flint glass vials, with butyl rubber stoppers and aluminum seals.

7.4.4 Storage and Stability

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

Shelf life

Unopened vial 2 years.

After opening:

From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately.

After preparation of infusion

From a microbiological point of view, the product should be used immediately.

If not used immediately, chemical and physical in-use stability of OPDIVO has been demonstrated for 24 hours at 2°C to 8°C protected from light and a maximum of 8 hours at 20°C-25°C and room light (this 8-hour period of the total 24 hours should be inclusive of the product administration

7.4.5 Compatibility

No incompatibilities between Nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

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7.4.6 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.4.7 Availability

Nivolumab will be provided by Bristol-Myers Squibb.

7.4.8 Preparation

Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.

*Note: Mix by **gently** inverting several times. **Do not** shake.*

Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection

Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

Note: It is not recommended that so-called “channel” or pneumatic tube systems are used to transport prepared infusions of nivolumab.

Attach the IV bag containing the nivolumab solution to the infusion set and filter.

At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Please refer to the current Investigator Brochure. Due to parameters surrounding the use time of nivolumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP].

After nivolumab (BMS-936558-01) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. Please refer to the Investigator Brochure for the details regarding storage, handling, and preparation of nivolumab.

7.4.9 Nivolumab Administration

Nivolumab is to be administered as an approximate 30-minute IV infusion, using a volumetric

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pump with a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at 240 mg. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Nivolumab will be given every two weeks at a dose of 240 mg. If an acute infusion reaction is noted, then acetaminophen/paracetamol 325 to 1000 mg PO and/or diphenhydramine 50 mg PO may be administered prior to nivolumab infusion. Corticosteroids (up to 25 mg of SoluCortef of equivalent) may also be used.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20°25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

7.4.10 Nivolumab Ordering

It is possible that sites may have more than one clinical study on the same drug ongoing at the same time. It is imperative that only drug product designated for this protocol be used for this study.

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

Please allow for 5-7 business days for the shipment of drug.

Initial Orders

- Following submission and approval of the required regulatory documents, BrUOG will activate each site, which will allow a supply of nivolumab (when applicable) to be ordered by the investigational pharmacist via the BrUOG 379 (CA209-79E) drug order form.
- It is required that the box “request for initial drug supply” be checked, the investigator address be confirmed as correct (if pre-populated) or populated (if blank), and that the # of vials being requested be documented on the form.
- Once complete, email the form to the email addresses on the drug order form: distribution.allentown@thermofisher.com and Cc bruog@brown.edu.
- Nivolumab:
 - Nivolumab will be supplied in 100 mg vials.
 - The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not

patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.

- When drug is received, it is required that an email be sent to bruog@brown.edu to alert BrUOG the order was received.
- Take note that drug should be transferred to +2°C/+8°C storage immediately upon receipt
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing

Re-Supply

- Drug re-supply request should be requested using the BrUOG 379 (CA209-79E) drug order form and allowing for 5-7 business days for drug shipment. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.
- It is required that the box “request for resupply” be checked, the investigator address be confirmed as correct (if pre-populated) or populated (if blank), and that the # of vials being requested be documented on the form.
- Once complete, email the form to the email addresses on the drug order form: distribution.allentown@thermofisher.com and Cc bruog@brown.edu.
- When drug is received, it is required that an email be sent to bruog@brown.edu to alert BrUOG the order was received.

Drug Excursions

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form. Please cc bruog@brown.edu on all drug excursion emails

Questions on drug expiration, delayed shipments etc:

- Send an email to Rashmi.gadkari@bms.com, and cc' bruog@brown.edu
- For questions on drug destruction please refer to 7.1.11 as this needs to be communicated directly with BrUOG only

7.4.11 Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

7.4.12 Destruction and Return

At the end of the study, unused supplies of nivolumab will be destroyed according to institutional policies once BrUOG confirms and approves destruction. BrUOG will obtain approval to destroy

from BMS. Destruction will be documented in the Drug Accountability Record Form and the form will be routed to BrUOG. Each participating hospital and pharmacy must submit, up front and throughout the trial, the most up to date drug destruction policy, to BrUOG.

Drug that is used (partially used vial for examples), can be destroyed in real-time as per the pharmacy destruction policy and do not need to be tracked on the accountability log.

Expired drug: Contact BrUOG to provide the number of expired vials and the current accountability logs. BrUOG will obtain approval to destroy drug and will communicate approval to the pharmacy. BrUOG will then require submission of the drug accountability log, documenting the drug destruction of expired material.

8 STUDY PROCEDURES

On days when ONC201 and nivolumab are administered on the same day, ONC201 should be administered within 30 minutes after completion of nivolumab

The day an assessment (PE, Lab, scan etc) is performed is considered day 0 for counting. For example, labs done on a Friday can be used for dosing Monday as this is within 3 days.

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy, unless otherwise specified below. Scans must be done <u><28</u> days prior to registration.	
Baseline labs are required within 14 days of registration. HCG is 7 days day 1 (of within 7 days of day -7 run-in for phase Ib). TSH within 28 days registration. Hepatitis required within 4 weeks registration	Pre- Study to be sent to BrUOG with results prior to registration
Informed consent(within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X
Archival tissue	X
Baseline biopsy (At least 3-6 cores to Dr. El Deiry's laboratory post consent and prior to ONC201) ^{12,13}	X
Demographics	X
Medical history ⁸	X
Concurrent meds ^{8,17}	X
Physical exam ⁸	X
Vital signs ^{1,8}	X
Height ⁸	X

Weight ⁸	X
Performance status ⁸	X
CBC w/diff, plts ^{4,8}	X
Serum chemistry ^{5,8}	X
Hepatitis panel HBsAg, HCV Ab, if positive HCV Ab then order HCV RNA testing ⁸	X
TSH and coagulation ^{6,8}	X
B-HCG ^{7,8}	X
PK plasma ⁹ (Phase IB patients only)	X
Blood sample for PD ¹⁰	X
CfDNA ¹¹	X
Adverse event evaluation ^{2,8}	X
EKG	X (within 8 weeks first dose)
Tumor measurements	X
CT Chest, Abdomen. and Pelvis (MRI of the abdomen/pelvis may substitute for CT of the abdomen/pelvis) ³	X
Brain MRI for patients with treated brain mets, scan must have been done post completion of treatment for brain mets ³	X
Bone scan or bone X-Ray or PET scan for patients with bone metastases ³	X

During treatment:

The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months, as determined by the investigator. Follow-up for all patients will be approximately 6 months.

The study is expected to be completed over an approximate 3.5-year period

Exam	Day -7	Cycle 1 ⁸ Pt to be seen as noted in table below	Cycle 2 Pt to be seen as noted in table below	Cycles 3-on, assessments Pt to be seen as noted in table below	Off study ¹⁴ (post completion of entire cycle) + 7 days	30 day (+ 1 week) and 100 days (+ 1 week)	Follow-up ¹⁵
Physical & HP (H&P due day 1, EOT and 30	X	Days 1, within 3 days	X within 3 days of	X within 3 days of dosing day 1	X	X	

day)		D15 (pre-nivo)	dosing day 1				
Vitals ^{1,8}	X	Days 1, within 3 days D15 (pre-nivo)	X within 3 days of dosing day 1 and day 15	X within 3 days of dosing day 1 and day 15	X	X	
Conmeds ¹⁷	X	Days 1, within 3 days D 15 (pre-nivo)	X within 3 days of dosing day 1 within 3 days of dosing day 1 and day 15	X within 3 days of dosing day 1 within 3 days of dosing day 1 and day 15	X	X	
PS	X	Days 1, within 3 days D 15 (pre-nivo)	X within 3 days of dosing day 1	X within 3 days of dosing day 1	X	X	
AE assessment	X	Days 1, within 3 days D 15 (pre-nivo)	X within 3 days of dosing day 1 within 3 days of dosing day 1 and 15	X within 3 days of dosing day 1 within 3 days of dosing day 1 and 15	X	X	
DLT assessment	X	Days 1, within 3 days D 15 (pre-nivo)	X (DLT assessment completed pre-cycle 2 day 1)				
EKG ¹⁶		as clinically indicated	as clinically indicated	as clinically indicated	as clinically indicated		
CT C/A/P ³			At week 8 (+1 week) ³	Every 8 weeks (+1 week) ³	X unless one was completed in prior 4 weeks		X ³
Brain MRI for patients with brain mets 3			X	X	X unless one was complet		X ³

					ed in prior 4 weeks		
Bone scan or bone X-Ray for patients with bone metastases ³		X	X	X unless one was completed in prior 4 weeks		X ³	
CBC w/diff, plts ^{4,8}		⁸ Weekly within 24 hours of dosing each day	X within 3 days of dosing day 1 and day 15	X within 3 days of dosing day 1 and day 15	X		
Serum chemistry ^{5,8}		⁸ Weekly within 24 hours of dosing each day	X within 3 days of dosing day 1 and day 15	X within 3 days of dosing day 1 and day 15	X		
TSH and coagulation ^{6,8}		⁸ X D1 only	X within 3 days day 1 only	X within 3 days day 1 only	X		
HCG ^{7,8}		X ^{7,8}	X	X			
PK plasma ⁹ (Phase IB patients only)	X ⁹	X ⁹ See schedule for all requirements D1,2,3,7	X ⁹ See schedule for all requirements D1,2,3,7	X ⁹			
Blood sample for PD ¹⁰	X ¹⁰	X ¹⁰ See schedule for all requirements D1,2,3,7	X ¹⁰ See schedule for all requirements D1,2,3,7	X ¹⁰			
cfDNA ¹¹		X prior to D15 dosing	X	X			
Tumor biopsy ¹³⁺¹²			Week 8 (+/- 7 days)		Biopsy at progression if patient has not progressed ¹³		

Survival and disease status							X ¹⁵
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*ONC201 is to be taken by patient in front of research staff day -7, day 1, day 8, day 15, day 22 in cycle 1.

¹Height, weight, blood pressure, pulse, temperature and respiratory rate. Pulse oximetry should be performed as clinically indicated.

² Toxicity assessments must be obtained within 14 days prior to initiation of protocol treatment

³ Radiological tumor assessments will be performed at baseline within 28 days of registration (all imaging) and subsequently every 8 weeks (+1 week), until progression of disease (see information on patients remaining on study post PD). Patients with stable scans at the first restaging may have restaging scans performed every 8 weeks at the discretion of the investigator, including in the follow-up time-period. **If patients come off study for progression, imaging will be stopped. CT C/A/P should be used for imaging**, if an alternative imaging modality is used at baseline, the same imaging technique must be used throughout the study duration. Patients who continue treatment beyond initial PD, will require a repeat radiographic assessment within 8 weeks (\pm 7 days) of initial PD to determine whether there has been a decrease in the tumor size or further progression, defined as an additional 10% increase in tumor burden from time of initial PD. Time to progression will be defined at the first time point of PD. Patients with brain or bone metastases at baseline, imaging post baseline, with brain MRI or bone scan, to occur as per institutional practice. When completed, site is required to be submit scans to BrUOG.

⁴ Hematology – CBC with PLT differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil).

⁵ Serum chemistry - K+, Na+, Ca++, Mg++, LDH, ALT, AST, total bilirubin, creatinine, amylase, alkaline phosphatase bicarbonate, phosphorus, glucose, BUN, albumin, and total protein. CEA, to be drawn monthly.

⁶ Coagulation - PT, PTT. With Coag labs, TSH will also be drawn Q monthly with pre-cycle labs

⁷ Serum or urine pregnancy test (women of childbearing potential) required within 7 days prior to day -7, Also required every 4 weeks (+/- 1 week) while on-study. Cycle 1 day 1: required HCG for all women of child bearing potential within 24 hours (1 day) prior to dosing day 1 cycle 1 only and confirmation of negative HCG test required to be sent to BrUOG. Patients with a positive test are required to be taken off study prior to any dosing on study.

⁸ If screening labs are performed greater than 14 days prior to Cycle 1 D-7, labs must be repeated on Cycle 1 D-7 and must meet eligibility criteria. The patient may not start on study treatment until Cycle 1 D-7 labs meet eligibility criteria. If screening labs are performed within 14 days prior to Cycle 1 D-7, and meet eligibility criteria, labs do not need to be repeated on Cycle 1 D-7 unless the investigator believes they are likely to have changed significantly. History, AE & concomitant medication assessment, vitals, weight, height and performance status can be used from screening for cycle 1 D-7 if they were within the 14-day screening period (14 days from day 1). A physical exam within 7 days prior to cycle 1 D-7 can be utilized.

⁹ PK plasma, (phase IB patients only):

Blood draws taken at baseline (pretreatment- with screening labs).

Then C1: Day 1 post ONC201 at 30 min+/- 15min, 2 hours +/-30 min, 4 hours +/- 30min, 6 hours +/- 30 min, 24 hours +/- 1 hour, 48 hours +/- 1 hour, 7 days (-). (this is day 8 pre-dosing ONC201).

Then C2: Day 1 post ONC201 at 30 min+/- 15min, 2 hours +/-30 min, 4 hours +/- 30min, 6 hours +/- 30 min, 24 hours +/- 1 hour, 48 hours +/- 1 hour, 7 days (-).(this is day 8 pre-dosing ONC201).

Cycle 3-12: Pre-dosing

Use one K2EDTA tube, 5mL sample: Tube should be gently inverted 8 times after draw and maintained at room temperature. Blood must be sent to research lab immediately after collected at the ambient temperature.

¹⁰ PD samples: all patients: Blood draws taken at baseline (pretreatment- with screening labs).

Cycle 1: Day 1: 6 hours post ONC201 +/- 30 min, 2 days post, 3 days post, 7 days post (this is day 8 pre-dosing ONC201)

Cycle 2: Pre-dosing day 1, 6 hours post ONC201 +/- 30 min, 2 days post, 3 days post, 7 days post (this is day 8, pre-dosing ONC201)

Cycles 3-12: Pre-dosing day 1. Patients remaining on study post 12 cycles, will have samples drawn prior to dosing day 1 of each cycle.

Use one red-top tube (no anti-coagulant), let sample clot, there is no processing. Blood must be sent to research lab immediately after collection at ambient temperature.

¹¹ cfDNA: blood to be collected at baseline (pre-dosing ONC201, prior to day -7 cycle 1) and prior to ONC201 and Nivolumab (twice a cycle with pre-Nivolumab labs) cycles 1-6. Cycles 7-on: CfDNA will be collected pre-dosing each cycle day 1 only. CfDNA will not be collected once patient progresses. If patient remains on study post 12 cycles, cfDNA will only be drawn pre-dosing day 1 of each cycle: **Collect CfDNA whole blood sample in 1 K2EDTA tube. Post collection, invert sample 8-10 times and let site at room temperature. See section 11.1.3.**

¹² Subjects providing informed consent will have tumor biopsy performed pre-treatment, at approximately 8 weeks when the first tumor imaging assessment is performed, and at the time of progression. For those patients whose disease is progressing at the first post-treatment imaging assessment at 8 weeks they will only have 2 biopsies.

¹³ Tissue from a biopsy (at least 3-6 cores in 10% neutral buffered formalin) will be obtained by radiologic guidance and sent to the laboratory of Dr. El-Deiry. Only 2 biopsies will be required for patients who progress at the end of cycle 2.

¹⁴ Off-study evaluation to occur post completion of entire cycle. Follow-up visits or other contact are required in order to identify SAEs during the first 100 days (+1 weeks) following the end of study treatment (Nivolumab, or ONC201), respectively. There will be a safety visit at 30 days (+1 week) and 100 days (+1 week) time points. SAEs need to be reported after 100 days if the SAE is thought to be related to study treatment. 30-day and 100-day safety evaluation time points required for all patients who receive at least one dose of drug on BrUOG 379, unless they withdraw consent.

¹⁵ Survival and disease status will be collected for all patients who receive at least one dose of ONC201 once they come treatment (unless they withdraw consent), approximately every 3 months for (+/- 1 month) 6 months

¹⁶ EKG registration and as clinically indicated. Any findings from EKGs collected after initiation of study treatment will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

¹⁷ Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the CRF from screening through 100 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

9 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance.

In the absence of treatment delays due to adverse event(s), treatment with nivolumab may continue as indicated in each cohort or until one of the following criteria applies:

- Disease progression (see information on patients remaining on study post progression)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Participant demonstrates non-compliance with treatment regimen and/or required study evaluations
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Any required toxicity reason as noted in prior sections of the protocol requiring the patient stop treatment
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing
- Oncoceutics decision to forgo further drug development of ONC201

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

10 Efficacy Evaluations

Tumor assessment for solid tumors will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans (when applicable); brain CT or MRI scan for patients with known brain metastases or those with suspected brain metastases; bone scan and/or bone x-rays for patients with bone metastases, if applicable. CT (or MRI) of chest, abdomen and pelvis, will be used for response.

Antitumor activity for patients with solid tumors will be assessed through radiological tumor assessments conducted at baseline, at the end of every other cycle (every 8 weeks), whenever disease progression is suspected (e.g., symptomatic deterioration), and at the time of withdrawal from the study (if not done in the previous 4 weeks).

Assessment of response in these patients will be made using RECIST version 1.1. All patients' files and radiologic images must be available for source verification.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

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

Treatment Beyond Disease Progression (also see information below on modified immune related

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response criteria)

Accumulating evidence indicated a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).

However, modification to these criteria will be employed to minimize the possibility that therapeutic agents that induce T cell infiltration into tumors as an early manifestation of anti-tumor effect could be erroneously interpreted as disease progression on imaging and result in premature discontinuation of a therapeutically effective agent.

Therefore, the protocol allows for patients to remain on study beyond initial progression if all of the following criteria are satisfied (and documented by treating MD and submitted to BrUOG):

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesions
- No more than 4 new lesions included in the sum.

It is not required that patients be kept on study after initial progression.

If the CT scan shows progression and the treating physician recommends continuing protocol treatment until a subsequent CT scan, this must be discussed with the patient and decisions to continue treatment beyond initial progression will be documented in the study records.

For patients who continue treatment in the case of initial radiologic progression, a repeat CT scan will be obtained within 8 weeks (± 7 days) of the initial detection of PD to determine whether there has been a decrease in the tumor size or further progression, defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions, increase in the sum of the diameters of new measurable lesions compared to the time of initial PD, and/or unequivocal progression in non-target lesions (compared to the time of initial PD).

- **Study treatment should be discontinued permanently upon documentation of further progression.**
If patient has **not** additional progression (10%) they can stay on treatment and continue on with study imaging as per the protocol time frames. However, if they subsequently progress by 10% at any time after, they must come off study.
- If SD is documented, patients will be allowed to continue on study treatment. However, if they subsequently progress by 10% at any time after, they must come off study.
For patients who experience a PR or CR (compared to baseline CT), they will continue treatment. They will be recorded as a **delayed response**

Definitions

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

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

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 or ≥ 10 mm with CT scan (preferred), MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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. NOTE: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Methods for Evaluation of Disease

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

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (inclusive of cervical masses and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal

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

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

- (a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- (b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- (c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

PET-CT. the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements and will not be used on this trial.

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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).

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

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

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

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

Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	≥ 4 wks Confirmation**
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline**
PD	Any	Yes or No	PD	
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	no prior SD, PR or CR

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

Note: Participants 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.

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

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

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

Modified immune-related response criteria (irRC), derived from RECIST 1.1

This irRC classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bidimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 8 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by $\geq 20\%$.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.

Overall irPR: Sum of the longest diameters of target and new measurable lesions decreases $\geq 30\%$.

Overall irSD: Sum of the longest diameters of target and new measurable lesions neither irCR, irPR,

(compared to baseline) or irPD (compared to nadir).

Overall irPD: Sum of the longest diameters of target and new measurable lesion increases $\geq 20\%$ (compared to nadir). It is recommended that overall irPD be confirmed by a follow-up CT at least 4-12 from the date first documented.

Overall responses derived from changes in index, non-index, and new lesions are summarized in the table below.

Overall Responses Derived from Changes in Index, Non-Index, and New Lesions

Measurable Response	Non-Measurable Response		Overall Response Using Modified irRC
Index and New, Measurable Lesions	Non-Index Lesions	New, Non-Measurable Lesions	
Decrease 100%	Absent	Absent	irCR ²
Decrease 100%	Stable	Any	irPR ²
Decrease 100%	Unequivocal progression	Any	irPR ²
Decrease $\geq 30\%$	Absent / Stable	Any	irPR ²
Decrease $\geq 30\%$	Unequivocal progression	Any	irPR ²
Decrease $< 30\%$ to increase $< 20\%$	Absent / Stable	Any	irSD
Decrease $< 30\%$ to increase $< 20\%$	Unequivocal progression	Any	irSD
Increase $\geq 20\%$	Any	Any	irPD

¹ Decreases assessed relative to baseline

² Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 8 weeks apart).

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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Pharmacokinetic Evaluations

During phase IB, plasma samples will need to be prepared from blood collected in K2EDTA tubes at baseline (pre-cycle 1 day 1), day 1: 30 minutes, 2, 4, 6, 24, 48, and 168 hours following the first two cycles of ONC201 and pre-dose on day 1 of subsequent cycles (through cycle 12 only). See schedule of evaluations for windows on each draw.

Pharmacokinetic samples will be collected and stored in the laboratory of Dr. Wafik El Deiry and processed at a later time.

Collect PK samples in one K2EDTA 5mL tube. Gently invert the tube 8 times after draw and maintain at room temperature.

One K2EDTA tube (5mL) will be collected per time point. Each tube will be labeled as follows:
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Patient initials

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Patient study number

PK sample

Time point

Time 24-hour clock

As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bio-analytical method. These data will be used for exploratory purposes and will not be included in the clinical report.

Prior to transporting samples, an email is to be sent from a member of the Lifespan Oncology Clinical Research Office to a member of Dr. El-Deiry's lab (Email: lanlan_zhou@brown.edu) at least 24 hours prior to the collection of the sample(s). The email is to reference the patient initials and BrUOG 379 patient number, time point and samples. The lab will be informed that the sample will be transported post collection on <insert date>. This email is required to be de-identified and submitted to BrUOG with cycle data.

Blood must be sent to the research lab immediately after collection at ambient temperature. Please call Lanlan Zhou at 267-259-7571 when samples are available.

Lab address:

70 Ship Street

Room 537

Providence, RI 02912

11.1.1 Background

Molecular markers involved in the molecular mechanism of ONC201 will be assessed on available tumor tissue and serum specimens as described below.

11.1.2 Biomarkers in Blood: PD samples

In addition to pharmacokinetics, this study will preserve samples at the laboratory of Dr. El-Deiry to conduct future correlative assays to measure biomarkers of therapeutic response to ONC201 including molecular markers involved in the mechanism of action of ONC201. For each patient, 1 tube of 5 mL of blood will be collected in red-top tubes (no anti-coagulants).

During phase IB and II, blood samples for PD analyses will need to be collected at baseline (pre-cycle 1 day 1), day 1: 6 hours, 2, 3, and 7 days after ONC201 treatment for cycles 1 and 2, and at pre-dose on day 1 for cycles 3 and beyond. Caspase-cleaved cytokeratin 18 (cCK18) will be measured as a biomarker of epithelial cell apoptosis and prolactin will be measured as a surrogate biomarker of DRD2 antagonism (Diapharma; #P10011). The 7-day collection is the same as pre-dose after the first dose on the weekly ONC201 schedule (this aligns with day 8). See schedule of evaluations for windows on draws. Patients who remain on study post 12 cycles, PD samples will be drawn pre-dosing day 1 each cycle.

Each sample will be drawn in one red-top with no anti-coagulant. The sample should clot, there is no processing to be done prior to the transport of the sample to the laboratory.

One red-top tube with no anti-coagulant, will be collected per time point. Each tube will be labeled as follows:

BrUOG 379

Patient initials

Patient study number

PD sample

Time point

Time 24-hour clock

Analysis of circulating tumor cells for enumeration and molecular analysis is also permitted.

Prior to transporting samples, an email is to be sent from a member of the Lifespan Oncology Clinical Research Office to a member of Dr. El-Deiry's lab (Email: lanlan_zhou@brown.edu) at least 24 hours prior to the collection of the sample(s). The email is to reference the patient initials and BrUOG 379 patient number, time point and samples. The lab will be informed that the sample will be transported post collection on <insert date>. This email is required to be de-identified and submitted to BrUOG with cycle data.

Blood must be sent to the research lab immediately after collection at ambient temperature. Please call Lanlan Zhou at 267-259-7571 when samples are available.

Lab address:

70 Ship Street

Room 537

Providence, RI 02912

11.1.3 CfDNA:

Blood samples need to be collected for CfDNA analysis at baseline (pre-cycle 1 day 1), then every two weeks while on study cycles 1-6, pre-ONC201 and on same days as Nivolumab dosing (prior to dosing day 1 and day 15). In cycles 7-12, CfDNA will be drawn pre-dosing day 1 each cycle only. CfDNA will be drawn until progression. If a patient remains on study post 12 cycles, sample to be drawn prior to dosing day 1 each cycle only (cycles 13+).

Each tube will be labeled as follows:

BrUOG 379

Patient initials

Patient study number

CfDNA sample

Time point

Time 24-hour clock

Prior to transporting samples, an email is to be sent from a member of the Lifespan Oncology Clinical Research Office to a member of Dr. El-Deiry's lab (Email: lanlan_zhou@brown.edu) at least 24 hours prior to the collection of the sample(s). The email is to reference the patient initials and BrUOG 379 patient number, time point and samples. The lab will be informed that the sample will be transported post collection on <insert date>. This email is required to be de-identified and submitted to BrUOG with cycle data.

CfDNA samples: Whole blood to be collected in one K2EDTA tube each time point. Post collection, site personnel is required to invert sample 8-10 times and then let sit at room temperature until sent to laboratory. Blood must be sent to the research lab immediately after collection at ambient temperature. Please call Lanlan Zhou at 267-259-7571 when samples are available.

Lab address:

70 Ship Street

Room 537

Providence, RI 02912

11.1.4 Biomarkers in Tumor Biopsy

Archival Tissue:

Research Biopsies: patients will undergo up to 3 biopsies on study.

- 1) Prior to dosing: Required post consent and pre-ONC201 run-in dose
- 2) At the beginning of cycle 3 (approximately 2 months) to align with imaging
- 3) If patient was found to not progress at 2 months (1st scan), then 3rd biopsy would be completed at time of progression (if patient progresses during follow-up time period). This biopsy is optional.

Tumor biopsies will be taken (pre-treatment and at the first imaging assessment post-treatment at 8 weeks of the combinatorial regimen, and again at the time of progression).

Tumor biopsies will be performed using 18G core biopsy needles (or as per standard radiologic procedures) and limited to 1–2 passes for each sample to reduce risk of hemorrhage and fine needle aspirations using 23G needles (or as per standard radiologic procedures) with immediate bedside cytopathological confirmation of presence of tumor cells.

Based on some preclinical studies, the 48 post-treatment time point is adequate to measure

induction of ATF4 & CHOP, as well as DR5 & TRAIL induction. Preclinical studies with ONC201 have implicated many proteins such as ATF4, CHOP, DR5 and TRAIL as drivers of the anti-tumor activity of ONC201. Changes in the expression of these markers will be assessed by immunohistochemistry at baseline and post-treatment. In addition, changes in key apoptotic proteins such as caspases and PARP will be carried out. Thus, we will correlate clinical outcomes with tumor & blood biomarkers including cancer stem cells, signaling intermediates and inhibitors, NK cells, TRAIL, granzyme, perforin and M30. NK cells in blood will be assessed in the phase Ib portion at similar time points as PK studies and then later in phase II.

Tissue biopsies will be subjected to immunohistochemistry for CHOP (Proteintech; # 5204-1-AP), DR5 (Novus; NB100-56618), CD56 (BioLegend, Catalog X), Granzyme B (Abcam; Catalog X) and TUNEL (Novus; #NBP2-31164) as per the manufacturer's instructions on slides prepared from formalin-fixed paraffin-imbedded tissue. NGS and RNA-seq will be performed on pre- and post-treatment biopsies looking for markers of sensitivity as well as mechanisms of resistance. A major goal is to understand the differences between responders and non-responders. Researchers will analyze T-cell and NK cell content of the tumor biopsies. PD1 and PD-L1 testing will also be performed.

For tissue from research only biopsy:

The research staff is to contact Dr. El Deiry's laboratory (to submit de-identified email chain with data to BrUOG) at least 24 hours prior to collection of a research only biopsy. Dr. El-Deiry's laboratory will be contacted by a member of the research team once the biopsy has been completed to retrieve the biopsy specimen (Email: lanlan_zhou@brown.edu). Once the biopsy is complete, the Cancer Center research staff will be notified for pick-up of material. The tissue must be labeled with study number (BrUOG 379), patient initials, patient study number and time point.

Each tissue biopsy is to include 3-6 cores and be stored in 10% neutral buffered formalin.

Tissue to be sent to the research lab once collected. Please call Lanlan Zhou at 267-259-7571 when tissue is available.

Lab address:
70 Ship Street
Room 537
Providence, RI 02912

12 ADVERSE EVENT REPORTING: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

12.1 Expected Toxicities

Adverse Event List(s) for Nivolumab

Categorization of AEs Potentially Associated with Nivolumab

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, the Sponsor identified select AEs based on the following 4 guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these are grouped into endocrine, GI, hepatic, pulmonary, renal, and skin select AE categories, respectively. The list of AEs belonging to select AE categories may evolve as more safety information becomes available in the nivolumab program.

Hypersensitivity/infusion reactions were also analyzed along with the select AE categories because multiple AE terms may be used to describe these events, and therefore, pooling of terms provides a more complete characterization of the events. Hypersensitivity/infusion reactions do not, otherwise, meet criteria to be considered select AEs.

Serious Adverse Events Reported from Clinical Trials with Nivolumab Monotherapy

As of June 2017, the following serious AEs have been reported in clinical studies in which nivolumab was given as monotherapy. The frequency of ADRs is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); and very rare ($< 1/10,000$). For further information, including SAEs that are rarely associated, please reference the IB.

The following **common** SAE is associated: pneumonitis, diarrhea

The following **uncommon** SAEs by system organ class are associated:

- Endocrine: Adrenal insufficiency, Hypothyroidism
- Gastrointestinal: Abdominal pain, Colitis, Diarrhea, Nausea, Pancreatitis, Vomiting
- General and Administrative Site Conditions: Mucosal inflammation, Pyrexia
- Hepatobiliary: Abnormal hepatic function

- Immune system: Hypersensitivity
- Injury, Poisoning and Procedural Complications: Infusion-related reaction
- Metabolism and Nutrition: Dehydration, Hyperglycemia
- Neurologic: demyelinating polyneuropathy, myasthenic syndrome
- Renal and Urinary: Acute renal failure, Tubulointerstitial nephritis
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, Hypoxia, Interstitial lung disease, Lung infiltration, Respiratory failure

Nonserious Adverse Events Reported from Clinical Trials with Nivolumab Monotherapy

As of June 2017, the following nonserious AEs have been reported in clinical studies in which nivolumab was given as monotherapy. The frequency of ADRs is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); and very rare ($< 1/10,000$).

The following **very common** nonserious AEs are associated: Fatigue, Diarrhea

The following **common** nonserious AEs are associated: Arthralgia, Asthenia, Cough, Decreased appetite, Pyrexia, Rash, Nausea, Pruritus

A complete list of adverse events observed with nivolumab are detailed in the Investigator's Brochure (IB).

12.2 Expected list of toxicities ONC201:

ONC201 is being evaluated in multiple on-going clinical trials. As of March 15, 2019, 150 patients have been treated with ONC201: 63 patients were male and 87 were female. The age ranged from 2 to 85 years, with 40 (27%) of patients < 18 years old. Seventeen patients received ONC201 on a Q3W schedule, 133 patients received ONC201 on a Q1W schedule. Adults were administered a dose of 625 mg, while children (< 18 years) were dosed from 125 mg to 625 mg depending on body weight.

ONC201 has been well tolerated across the various Phase I clinical trials and administration schedules with dose levels ranging from 125 mg to 625 mg. Only 1 dose reduction (625mg to 500mg) occurred in 1 patient with a Grade 3 neutropenia assessed by the PI as possibly related to ONC201. However, upon re-challenge neutropenia did not recur.

Some patients who received ONC201 have experienced mild or moderate adverse events that were attributed as possibly related to ONC201: fatigue, abdominal pain, fever, nausea, vomiting, anorexia, weakness, elevated serum amylase, neutropenia, bone pain, generalized weakness, allergic reaction, and ataxia.

In summary, ONC201 is well tolerated when administered once every week or once every three weeks at doses ranging from 125 mg to 625 mg.

Side effects seen in animals at exaggerated doses included the following:

- Nausea
- Salivation
- Vomiting
- Abnormal breathing
- Twitching
- Abnormal walking or standing
- Death

A complete list of adverse events observed with ONC201 are detailed in the Investigator's Brochure (IB).

12.3 Adverse Event Characteristics

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to 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 Nivolumab or ONC 201, whether or not considered related to Nivolumab or ONC 201. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication.

12.4 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

12.4.1 Attribution of the AE:

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

Suspected adverse reaction:

BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected.

As per 21 CFR 312.32 (a), the FDA has defined a suspected adverse reaction as any adverse event where there is reasonable possibility that the drug may have caused the adverse event. A reasonable possibility means there is evidence suggesting a causal relationship between the drug and the adverse event.

A suspected adverse reaction outlines the possibility of the causal relationship between the event and the drug, whereas an adverse reaction means the drug caused the event.

12.4.2 Serious Adverse Events (SAE) Definition

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusion support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

12.4.3 Events requiring reporting as an Important Medical Event:

- **Potential drug induced liver injury** (DILI) is also considered an important medical event.

Potential drug induced liver injury is defined as:

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

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

- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer (a second primary, excluding non-melanoma skin cancer) are not always serious by regulatory definition, these events must be handled as SAEs.
 - **Pregnancy:** see section for information
 - 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.

NOTE: The following hospitalizations are **not considered SAEs**:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered “important medical event” or event life threatening)
- elective surgery, planned prior to signing consent and which would have been documented to BrUOG at time of registration (otherwise it will be a SAE)
- admissions as per protocol for a planned medical/surgical procedure per study
- routine health assessment requiring admission for baseline/trending of health status (ie, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases and which would have been documented to BrUOG at time of registration
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (ie, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient’s study participation will be recorded in the source documents.

12.5 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS

Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 100 days (+1 week) after the last treatment (Nivolumab or ONC201, whichever is last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first. There will be a safety visit at 30 days (+1 week) and 100 days (+1 week) time points.

12.5.1 Pregnancies

Pregnancies occurring while the subject is on study drug or within 100 days (+1 week) after the subject’s last treatment (Nivolumab or ONC201, whichever is last) are considered expedited reportable events. If the subject is on active treatment, the treatment is to be discontinued immediately. The pregnancy must be reported to the Brown University Oncology Research Group, by the site, immediately (within 24 hours of the site being made aware), via the site completed BMS pregnancy reporting Form **and** a 3500A MedWatch form (site to submit to BrUOG), and BrUOG will in turn report to BMS and Oncoceutics immediately (within 1

working day and once in receipt of the site submitted SAE forms). Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on treatment (Nivolumab and/or ONC201), or within 100 days (+1 week) of the subject's last treatment (Nivolumab or ONC201, whichever is last), are considered immediately reportable events. Treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to BMS Drug Safety and Oncoceutics immediately by facsimile, email, or other appropriate method (to be done by BrUOG), using the required reporting forms (Forms to be completed by site and sent to BrUOG).

The Investigator will follow the subject until completion of the pregnancy, and must notify BMS and Oncoceutics (by informing BrUOG) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG who will then report to BMS and Oncoceutics by facsimile or email within 1 working day of being made aware of the event via the sites formal submission of the SAE pregnancy forms).

The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 100 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 100 days that the Investigator suspects to be related to the in-utero exposure to the study drug should also be reported. In the case of a live "normal" birth, BMS and Oncoceutics should be advised as soon as the information is available (BrUOG will advise BMS once information is submitted to BrUOG).

12.5.2 Serious Adverse Event Reporting Procedures

All pregnancies or suspected pregnancies, including suspected fetal exposure or neonatal deaths must be reported to the Brown University Oncology Research Group immediately (within 24 hours of being made aware of the event). BrUOG will report all pregnancies to BMS and Oncoceutics within 1 working day, and once being made aware of the event once in receipt of the site submitted required reports. All other SAEs are to be announced via email to BrUOG within 24 hours of being made aware of the event and the site has 5 business days (from being made aware of the event) to send the written MedWatch 3500A report to BrUOG, who will then report the SAE to BMS product safety and Oncoceutics within 1 working day of being in receipt of the completed and signed MedWatch report (submitted to BrUOG from the site). Initial SAE information and all amendments or additions must be recorded on an SAE Form and faxed or emailed to BMS and Oncoceutics (to be done by BrUOG).

BMS Drug Safety and Oncoceutics Contact Information: (to be reported to by BrUOG)

BMS SAE EMAIL ADDRESS: Worldwide.Safety@BMS.com

Oncoceutics EMAIL ADDRESS:

Pharmacovigilance@oncoceutics.com

A copy of the fax transmission or email confirmation of the SAE report to BMS and Oncoceutics should be attached to the SAE and retained with the study records at BrUOG.

The principal investigator (or his designee) has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, BMS, Oncoceutics and all sites participating in the trial. All SAE reports will be forwarded to BMS Product Safety and Oncoceutics by BrUOG. All events must be reported by the investigator utilizing the Form FDA 3500A (MedWatch Form). Sites must alert BrUOG to SAEs within 24 hours of being made aware of the event via phone or email, and the site will have 5 business days (from when site was made aware of the event) to submit formal signed report via the 3500A. BrUOG will then alert BMS and Oncoceutics within 1 business day of being in receipt of the signed MedWatch report. BrUOG will submit a SAE memo and MedWatch 3500A to the FDA within the reporting time frames.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report.

A final report to document discharge from hospital (or end of important medical event) is required.

All deaths during treatment or within 100 days (+ 1 week) following completion of active protocol treatment (Nivolumab or ONC201, whichever is last) must be formally reported to BrUOG within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study treatment (Nivolumab and/or ONC201), deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 100 days (+1 week) after the last treatment (Nivolumab or ONC201, whichever is last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first. There will be a safety visit at 30 days (+1 week) and 100 days (+1 week) time points.

Every adverse event, serious or non-serious, must be assessed by the investigator with regard to whether it is considered immune-mediated.

Serious adverse events occurring more than 100 days (+1 week) after study discontinuation need only be reported if a relationship to the study treatment (Nivolumab and/or ONC201) is suspected.

12.5.3 Types of Report: Guidelines for sites to report:

Telephone report: For SAE's contact the BrUOG office within 24 hours of learning of a SAE. For SAE notification: (initial and follow-up) contact BrUOG Central Office (401) 863-3000 (or via email), with 24 hour notice prior to submitting a SAE report.

Written report: Send the signed MedWatch 3500A form (and BMS pregnancy reporting form for pregnancies if applicable) within 5 business days of being made aware of the event to the BrUOG Central Office by email. For Follow-up reports, please submit the signed MedWatch 3500A when new information has become available and the event can be closed out.*Of note Oncoceutics will not receive BMS pregnancy form, just the Medwatch3500A*

Brown University Oncology Research Group

Phone: (401) 863-3000, Fax: (401) 863-3820

Emails: BrUOG@brown.edu

All deaths during treatment or within 100 days (+ 1 week) following completion of active protocol treatment (Nivolumab or ONC201, whichever is last) must be reported within 5 business days (from when site was made aware of the event) or as soon as the investigator is made aware of the event. If the death is thought to be related to the study treatment (Nivolumab and/or ONC201), **deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event. SAEs post 100 days since last dose of drug (+1 week) that are thought to be possibly related to study treatment** (Nivolumab or ONC201, whichever is last) **must be reported to BrUOG within the 5-business day time frame noted above.**

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy): if related to treatment regimen add to section C suspect product, if not related to any, add to concomitant section noting Lot #
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**

- **Action taken with Nivolumab and ONC201 as a result of the SAE and expectedness (based on IB and consent)**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to **each investigational product** (Nivolumab) and suspect medication/treatment (ONC201) and if event(s) is/are immune mediated
- Documentation if the event(s) are considered immune mediated
- Site to be clear to outline which events are being reports as serious
- Must be typed
- ****It is required that sites put the following numbers on the MedWatch form for tracking:**
 - **BrUOG 379**
 - **INSERT BMS tracking # CA209-79E**

A final report to document discharge from hospital (or resolution of important medical event) is required.

All SAE reports (initial or follow-up), must be signed by the treating physician or PI of the trial. Any SAEs that are signed and submitted to BrUOG, but do not include required reporting information, will be queried for updating to ensure all required information is included. In such instances, SAEs will be updated by the reporting site and re-submitted to BrUOG.

Follow-up information:

For any follow-up SAE report, submit a new MedWatch 3500A report; do not resubmit the initial report with any additions. The follow-up report must be submitted to BrUOG with subject identifiers (subject number, initials, and date of birth), protocol description and number (BrUOG 379 and tracking numbers(s) as noted above), suspect drug, a brief summary of previously reported SAE information, and any new information, including modification of prior events, causality, new serious events, discharge date, etc.

A final report documenting discharge date from the hospital is required.

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

12.6 BrUOG Responsibility Regarding Reporting:

The sponsor-investigator by way of BrUOG, the sponsor representative and central coordinating office, is required to promptly review all information relevant to the safety of the drug (21 CFR 312.32(b)).

Safety Reporting for IND Holders

In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND

must comply with following safety-reporting requirements:

The BrUOG Central Office will notify by fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 15 calendar days after initial receipt of the signed information, submitted to BrUOG by the site, as per regulatory requirements.

BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected (21 CFR 312.32 (c)(1)(i)). It is required that events that are suspected, serious and unexpected, be reported to the FDA via an IND safety report.

BrUOG will fax reports to the FDA for IND Safety Reports: to the CDER fax number.

SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. The FDA will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA (which will be sent to the MedWatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

- “IND safety report” for 15-day reports
- “Follow-up IND safety report” for follow-up information
- “7-day IND safety report” for unexpected fatal or life-threatening adverse reaction reports

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All SAEs that are serious and reasonably or probably related to the use of Nivolumab and/or ONC201 will be sent to: BMS and Oncoceutics

BrUOG will alert BMS and Oncoceutics to an SAE within 1 business day of being in receipt of the complete signed site submitted documentation.

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be sent to BMS and Oncoceutics, as well as any pregnancy occurring in association with use of a BMS and Oncoceutics Product to (of note do not submit BMS pregnancy form to Oncoceutics):

BrUOG will send to: BMS SAE Email Address: Worldwide.Safety@BMS.com

BMS SAE Facsimile Number: +1 609-818-3804

Oncoceutics contact: Pharmacovigilance@oncoceutics.com

12.7 IND Annual Reports, for IND study only

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to BMS as a supporter of this study

12.8 Adverse event updates/IND safety reports

BMS shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

13 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Khaldoun Almhanna, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is supported by BMS (the makers of Nivolumab) and Oncoceutics (the makers of ONC201).

13.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

13.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be created by Brown University Oncology Research Group, and approved by BMS and Oncoceutics. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and BMS and Oncoceutics of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, BMS and Oncoceutics. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

13.3 Protocol amendments or changes in study conduct:

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be created the Brown University Oncology Research Group, BMS, Oncoceutics and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, Oncoceutics and BMS

- Examples of amendments requiring such approval
- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group, Oncoceutics and BMS in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group, Oncoceutics and BMS must be notified and the IRB at the center must be informed immediately.

14 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

14.1 Good Clinical Practice:

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator Brochures. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Patient Confidentiality:

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from BMS, Oncoceutics or their designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.3 Protocol Compliance:

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from BMS, Oncoceutics and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to BMS, Oncoceutics and the regulatory authority (ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

14.4 On-site Audits:

Regulatory authorities, the IRB and/or BMS and/or Oncoceutics clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14.5 Drug Accountability:

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to BMS and Oncoceutics for disposal of the drug (if applicable and if approved by BMS and Oncoceutics for their respective drugs) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing Nivolumab and ONC201 will be treated and disposed of as hazardous waste in accordance with governing regulations.

14.6 Premature Closure of the Study:

This study may be prematurely terminated, if in the opinion of the investigator, Oncoceutics or

BMS, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator, Oncoceutics or BMS by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to BMS and Oncoceutics (unless another method if approved by the company (ies)

14.7 Record Retention:

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (Khaldoun Almhanna, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. BMS will notify the Principal Investigator if an application is filed.

15 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.

- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

16 DATA ANALYSIS/STATISTICAL METHODS

16.1 Sample Size Determination for Phase I

No formal sample size determination is possible for Phase I of this trial due to the inherent nature of Phase I de-escalation trials. If no DLTs are observed in the first 3 patients entered at the initial ONC 201 dose level (625mg weekly) then 3 additional patients will be entered on the phase IB portions to further assess safety and pharmacokinetics. The protocol includes 2 additional de-escalated levels that may be used dependent on toxicity.

16.2 Safety Analysis

The primary population for the assessment of the MTD is defined as all patients experiencing a DLT during DLT observation window (run-in dose day -7, cycle 1 to assessment pre-dosing cycle 2) following the first administration of the combination of ONC201 and nivolumab.

Patients receiving less than 80% of the ONC201 planned dose during the first cycle will not be evaluable for the assessment of the MTD provided that the dose reduction is not related to any-grade drug toxicity (if it is related to a toxicity- see DLT definition).

DLTs will be presented by dose level.

DLT definition:

Hematologic:

- Grade 4 neutropenia that persists for >7 consecutive days
- Febrile neutropenia (defined as neutropenia \geq Grade 3 and a body temperature 38.5°C)

- Grade ≥ 3 neutropenic infection
- Grade 4 thrombocytopenia (platelets $<25,000$ cells/mm 3) or Grade ≥ 3 thrombocytopenia with bleeding

Nonhematologic:

- Any other treatment related, clinically significant Grade ≥ 3 toxicity not classified under CTCAE blood or bone marrow with the exception of grade 3 nausea, vomiting, or diarrhea in patients who have received optimal treatment with antiemetics or anti-diarrheals and who do not downgrade to a grade 1 within 72 hours; Grade 4 (life threatening) diarrhea or vomiting will be considered DLTs, irrespective of the duration of the event. alopecia is not a DLT
- Delay of > 2 weeks secondary to a treatment related AE that is deemed possibly or definitely related to either drug
- Failure to receive at least 80% of the planned dose on ONC201 due to treatment related AEs (ONC201) in cycle 1 (5 doses ONC201 with run-in).

Although toxicities may be observed at any point during treatment, only those occurring during the defined DLT observation window of treatment that are considered DLTs will guide dose escalation decisions, expansion of a dose level, or evaluation of intermediate dose levels.

16.2.1 Early Stopping Rule for Safety for Phase II study

Formal early stopping rules will not be utilized. Safety in this trial is governed by the DLT rules and oversight provided by the BrUOG DSMB. It is anticipated that severe toxicity will not exceed 30%.

In the phase II cohort an additional 28 patients will be accrued so that a total of 34 patients will be treated at the RP2D (including 6 patients treated at the RP2D on the phase IB portion of the trial).

Accrual will be suspended for excess toxicity if over 9 of the initial 12 Phase II patients experience an event that was defined as a DLT in the phase I portion. The chance of early study suspension (i.e., ≤ 17 subjects accrued) is 50% if the true toxicity is 50% and 4.0% if it is 30%. Similarly, accrual will be suspended if, at any point among the 34 patients, 15 or more subjects are observed with an event that was defined as a DLT in the phase I portion. Suspension will occur, either early or finally, with probability 82% if true toxicity is 50% and 7.8% if it is 30%.

A patient experiencing a toxicity defined as a DLT, post cycle 2 (phase I) or in the phase II portion, is required to have treatment (both drugs) held, once the toxicity reduces to a grade 1 or less, dose reduce (ONC201) and resume treatment, even though it will no longer be defined as a DLT.

16.3 Efficacy Analysis for Phase II

All patients who have received a minimum of 1 cycle of study treatment, had baseline assessments

and at least one on-study tumor assessment will be considered evaluable for response.

Response rate is defined as the proportion of patients with a Complete (CR) or Partial Response (PR) relative to the total number of evaluable patients. Responses will be defined according to the RECIST version 1.1 guidelines for solid.

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or the withdrawal from the study. Stable disease will be considered the best response when observed at least after two months from baseline. Tumor responses will be analyzed in a descriptive manner. The number and percentage of objective response (CR+PR) will be tabulated. Response rate may be summarized with the corresponding 95% exact confidence interval.

Progression free survival will be defined as the number of days between the first treatment with protocol specified therapy and death or progression, whichever comes first. Individuals who are alive and progression free at last contact will be censored at that time.

Overall survival (OS) will be defined as the number of days between the first treatment with protocol specified therapy and death. Individuals who are alive at last contact will be censored at that time.

Progression free survival and overall survival time distributions in the Phase II study population will be summarized using the methods of Kaplan and Meier.

16.4 Primary Analysis for Phase II

Following completion of the Phase I trial, we will conduct a single-arm, double endpoint Phase II study to evaluate the efficacy of the promising treatment combination. In Phase II, we will evaluate the co-primary outcomes of response and Progression Free Survival (PFS), testing the composite null hypothesis that P_r , the chance of response, is at most 5% AND the chance of PFS at 3 months, P_s , is at most 50%. The alternative for which power is computed is that the P_r is at least 20% OR P_s is at least 71% (this corresponds to median PFS of 6 months, assuming an exponential model). Our double end-point design (Sill *et al.*, 2012) evaluates an initial cohort of 17 patients. If 1 of 17 respond or 4/17 are Progression Free (PF) at 3 months then recruitment will continue to 34 patients. The null is rejected if there are at least 5/34 responses or at least 22/34 patients PF at 3 mo. Statistics under independence of response and PFS at 3 months (i.e., $P_{rs} = p(\text{response AND PFS at 3 months}) = P_r * P_s$), as well as the most extreme forms of dependence, ($P_{rs} = \min(P_r, P_s)$ or $P_{rs} = \max(0, P_r + P_s - 1)$), were computed. Power: The design provides at least 80% power and at most 7.9% type I error. The chance of early stopping under the null is at least 52% and at most 10.7% under any alternative.

Pharmacokinetic Analysis

All patients who complete at least one day of PK blood sampling will be included in the PK analyses. Plasma concentration/time data of ONC201 obtained at the designated times will be summarized descriptively and presented graphically by dose and day of assessment. The concentration/time data of ONC201 will be analyzed using non-compartmental methods to obtain PK parameters in individual patients. These PK parameters include the maximum plasma

concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time curve to 24 hours (AUC_{24hr}) and area under the plasma concentration versus time curve to the time of the last measurable concentration (AUC_{last}). If data permit, area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F) and apparent volume of distribution (Vd/F) will be also estimated.

Individual values and descriptive statistics of these PK parameters will be provided by dose and day of assessment in tabular form.

To determine any interactions between ONC201 and nivolumab, plasma concentrations of both drugs will be monitored closely. Changes in PK parameters, such as T_{max} , C_{max} , λ_z , $t_{1/2}$, AUC_{last} , AUC_{inf} , C_{min} and, CL/F, of ONC201 will be compared between single agent ONC201 (run-in component) and ONC201+ nivolumab. Similarly, PK parameters of nivolumab will be compared to historical control (Gaudreault J, Cancer Chemother Pharmacol).

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APPENDIX A Eligibility CHECKLIST

BrUOG 379: Phase Ib/II investigator-initiated, single arm study of ONC201 plus Nivolumab in microsatellite stable (MSS) metastatic colorectal cancer (mCRC) patients

Inclusion criteria:

(y/n) Patients must have a histologically/cytologically-confirmed MSS primary colorectal adenocarcinoma tumor, with confirmation of being microsatellite stable.

(y/n) Radiographic or clinical evidence of metastatic disease that has progressed after at least 2 prior regimens. Prior bevacizumab, cetuximab, trifluridine and tipiracil, or regorafenib is allowed, prior FOLFIRI and FOLFOX treatment is required. (Treatment with a FOLFIRINOX regimen will count as 2 regimens). Prior treatment not required to be have been administered in the metastatic setting.

(y/n) Patients must have measurable disease by RECIST criteria

(y/n) All patients must have a tumor(s) located in an area that can be biopsied as confirmed by treating physician

(y/n) All patients must submit representative tissue from their malignancy if it is confirmed there is enough tissue from prior surgery or most recent biopsy. This can consist of archival tumor samples or tissue collected at biopsy to prove recurrence. In both cases, samples should consist of a formalin-fixed paraffin embedded (FFPE) tumor tissue block or at least 20 unstained slides (charged) of 4 μ M thickness sent to the lab address in section 11.1.4. Tissue located outside of Lifespan Cancer Institute hospitals must be confirmed as requested prior to enrollment.

(y/n) All previous therapies for cancer, including radiotherapy, major surgery and investigational therapies must be discontinued for \geq 14 days before the first dose of ONC201 (D-7 run in).

(y/n) All clinically significant adverse events related to any prior therapy must have resolved to Grade \leq 1 Common Terminology Criteria for Adverse Events (CTCAE v5.0), except alopecia or parameters defined in this eligibility list.

(y/n) Age \geq 18 years.

(y/n) ECOG performance status \leq 2.

(y/n) Adequate organ and marrow function as defined below:

a. Absolute neutrophil count \geq 1,000/mm³ without growth factor use \leq 7 days prior to treatment (this is Day -7) (y/n)

b. Platelets \geq 75,000/mm³ without platelet transfusion \leq 7 days prior to treatment (this is Day -7) (y/n)

c. Hemoglobin \geq 8.0 mg/dL without red blood cell transfusion \leq 7 days prior to treatment (this is Day -7) (y/n)

d. Total serum bilirubin \leq 1.5 X upper limit of normal (ULN) (y/n)

e. AST (SGOT)/ALT (SGPT) \leq 2 X ULN; \leq 5 X ULN if liver dysfunction is felt to be secondary to tumor burden within 14 days prior to treatment (this is Day -7) (y/n)

f. Serum creatinine \leq 1.5 X ULN (OR creatinine clearance \geq 60 mL/min/1.73 m²) within 14 days prior to treatment (this is Day -7) (y/n)

g. Serum or urine pregnancy test (for females of childbearing potential) negative \leq 7 days of treatment (this is Day -7) _____ (y/n)

_____ (y/n) Ability to understand and the willingness to sign a written informed consent document and comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

_____ (y/n) Female patients of child-bearing potential must be practicing an effective form of contraception from the time of informed consent and for the duration of the study treatment through 5 months after the last dose of drug (ONC201 or Nivolumab, whichever is administered last). The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

_____ (y/n) Male patients who are with women of child-bearing potential must be surgically sterile (provide date of surgery) or must agree to use effective contraception from the time of informed consent and for the duration of the study treatment through 7 months after the last dose of drug (ONC201 or Nivolumab, whichever is administered last). The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

_____ (y/n) Patients must agree to the required tumor biopsies to enroll in the trial. Pre-treatment biopsies can occur any time post consent and prior to run-in ONC201 dose, a second biopsy will be required at the end of cycle 2 to assess response biomarkers, a final biopsy is included at the time of progression to assess for resistance mechanisms. Only 2 biopsies will be required for patients who initially progress at time of 2nd biopsy.

Exclusion

_____ (y/n) Patients with symptomatic brain metastases are excluded. Patients with asymptomatic and treated CNS metastases may participate in this trial. The patient must have completed any prior treatment for CNS metastases $>$ 28 days prior to registration, including radiotherapy or surgery. Steroids for the treatment of brain metastasis are not permitted.

_____ (y/n) Patients with prior treatment with ONC201 or who have had prior therapy with nivolumab or 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 co-stimulation or immune check point pathways will be excluded

_____ (y/n) Active inflammatory gastrointestinal disease such as severe chronic diarrhea (unless related to underlying malignancy), gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study registration. Gastroesophageal reflux disease under controlled treatment with proton pump inhibitors is allowed.

_____ (y/n) Pregnant or breast feeding.

_____ (y/n) Current active treatment in another clinical study (treatment trial) within 14 days of D-7.

_____ (y/n) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics, hepatitis, active rheumatologic or collagen vascular disease, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

NOTE: Participants with active or a history of Hepatitis B or C infection as follows:

_____ (y/n) Active hepatitis B (positive hepatitis B surface antigen [HBsAg] or hepatitis C virus (HCV) (positive HCV RNA) are not eligible to participate.

(y/n) HBV carriers or those participants requiring antiviral therapy are not eligible to participate.

(y/n) Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA. If PCR is positive, they are not eligible to participate.

(y/n) Past HBV infection or resolved HBV infection are may be eligible on this trial provided the following criteria are met prior to randomization: Positive for hepatitis B core antibody (HBcAb), the absence of hepatitis B surface antigen (HBsAg), and no detectable HBV DNA in serum.

(y/n) Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. (testing is not required for eligibility).

(y/n) Any of the following in the previous 3 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism as defined by treating physician.

(y/n) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.

(y/n) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

(y/n) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day 1 of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

(y/n) Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer are excluded if there is any evidence of other malignancy being present within the last three years (2 years for invasive breast cancer). However, patients with a malignancy that is non-likely to require treatment, as per the treating physician, in the next 2 years, such as a completely resected, early stage breast cancer, or other malignancies treated with curative intent are eligible. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

(y/n) Prior treatment with immunotherapy for any cancer, including immune checkpoint inhibitors or anti-CTLA4 agents

(y/n) Participants who have received a live / attenuated vaccine within 30 days of first treatment.

Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>
2) Heme/Onc initial note	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>
3) Pathology Report(s)	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>
4) MRI/CT Report(s)	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>
5) Lab Source Document	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>
6) ICF signature page	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>
7) Other documentation	Enclosed <input type="checkbox"/> Not Enclosed <input type="checkbox"/> Not Applicable <input type="checkbox"/>

It is required that each item from schedule of evaluations be submitted to BrUOG along with confirmation via source to match each inclusion and confirm each exclusion criteria.

Most recent IRB approval date (whether this be the initial, latest amendment or CR): _____

Date of research biopsy pre-treatment: _____

Date of day -7 treatment: _____

Date of treatment day 1: _____

Hospital where patient will be treated with Oncologist: _____

Name of treating physician: _____

Your signature: _____

Appendix B

Agreement to Participate in a Research Study and Authorization for Use and Disclosure of Information

Phase Ib/II investigator-initiated, single arm study of ONC201 plus Nivolumab in microsatellite stable (MSS) metastatic colorectal cancer (mCRC) patients

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPITAL NAME> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPITAL NAME>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement that states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

Nature and Purpose

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Khaldoun Almhanna, in collaboration with the Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are invited to take part in a clinical trial, a type of research study, because you have advanced colon cancer. You previously received standard chemotherapy but your cancer has spread and become worse. The purpose of this research study is to test how safe and how well an investigational drug known as ONC201 works in combination with the immunotherapy drug

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nivolumab in treating advanced colon cancer.

“Investigational” means that the FDA (the U.S. Food and Drug Administration) has not approved ONC201 as a treatment for colon cancer or any other cancer. ONC201 is a newly discovered compound that may stop cancer cells from growing, however this is not yet known. This drug has been shown in laboratory experiments to use a new mechanism (way) that creates a response to kill cancer cells but not normal cells.

Nivolumab is a drug that helps stimulate your immune system to fight certain cancers. It is FDA approved to treat some forms of cancer such as lung cancer, kidney cancer, a form of skin cancer called melanoma and a rare form of colon cancer called “microsatellite unstable colon cancer”. However, nivolumab does not show activity against your form of colon cancer (microsatellite stable colon cancer) and is not FDA approved for your form of colon cancer. In the laboratory, Researchers are testing if ONC201 may help nivolumab be more effective in stimulating the immune system to treat cancer.

Bristol-Myers Squibb, a pharmaceutical company that makes the drug Nivolumab, is financially supporting this research study by providing the study drug nivolumab and funding for the study. Upon completion of the trial, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators. Your doctor is responsible to ensure that you receive appropriate standard of care or other appropriate treatment to treat your condition.

ONC201 is being supplied by the pharmaceutical company Oncoceutics, Inc.

Dr. Wafik El-Deiry is a person involved in this medical research study who owns a patent on the new drug being studied. Research studies like the one you are thinking about joining are done to determine whether the new drug is safe and effective. If the research in question shows that the new drug is safe and effective, Dr. El-Deiry may benefit financially from the success of this drug.

How Many People will take part in the Study?

It is expected that approximately 34 people will take part in this research study.

Explanation of Procedures

What will happen if I take part in this research study?

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests, while on the study. They are part of regular cancer care.

- **A medical history**, which includes questions about your health, current medications, and any allergies.
- **Safety evaluations**, which collects information on how you are feeling
- **Performance status**, which evaluates how you are able to carry on with your usual

activities.

- **An assessment of your tumor by CT (Computerized Tomography) scan**
- **Complete Blood Count (CBC) and serum chemistry blood tests** to determine your general health status and screen for certain diseases
- **Pharmacokinetic (PK) blood samples.** This looks at the movement and metabolism of the drug into and throughout the body. Each blood sample will be approximately 2 teaspoons.
- **Pharmacodynamic (PD) blood samples.** This looks at the effect of the drug on the body. Each blood sample will be approximately 2 teaspoons.
- **cfDNA blood samples.** This looks at the DNA fragments in the blood plasma. Each blood sample will be approximately 2 teaspoons.
- **Pregnancy test (blood),** if you are a female of child-bearing potential.
- **Electrocardiogram (ECG),** which measures the electrical activity of your heart
- **Tumor Biopsy:** A sample of your tumor from your initial diagnosis or the most recent biopsy procedure will be requested by your study doctor. Additionally, a biopsy will also be performed prior to starting treatment and post consent. A biopsy will be repeated approximately 2 months after you begin treatment on this study.

While on study:

Tumor Biopsy: A sample of your tumor will be biopsied prior to starting treatment and post consent. A biopsy will be repeated approximately 2 months after you begin treatment on this study. If at the time of the 2-month biopsy, your cancer progressed (worsened), no further biopsies will be taken. If your cancer is stable, there will be a third and optional biopsy performed if/when your cancer progresses during treatment or in follow up. Researchers at Rhode Island Hospital, Brown University, and collaborating laboratories will examine your tumor tissue to see how the study treatment may affect your cancer. If you choose to sign this consent form and participate in this trial, your doctors will also request a portion of your tumor tissue for storage for use in future research.

This is the first study testing the combination of ONC201 and nivolumab.

Phase Ib:

In the first part of the study (phase IB portion of the study), patients will be treated in groups of 3-6 patients to determine the best safe dose of the combination of ONC201 and nivolumab. The initial 3-6 patients will receive the recommended dosages of ONC201 (5 capsules) and nivolumab when each drug is administered alone. Patients will receive one dose of ONC201 alone and then will begin treatment approximately one week later with both ONC201 and Nivolumab. One treatment cycle will be 4 weeks. You will be given Nivolumab once every 2 weeks into your vein (by intravenous infusion). ONC201 will be given orally once a week using capsules.

If the side effects are too severe, the dosages will be lowered for the next 3-6 patients on the Phase IB portion until a safe dose is found.

Phase II:

Once the safe combined dose is found, in the phase II portion of the study, 28 patients be treated, using the dose found in the phase IB portion of the study.

Patients will receive one dose of ONC201 alone and then will begin treatment approximately one week later with both ONC201 and Nivolumab. One treatment cycle will be 4 weeks. You will be given Nivolumab once every 2 weeks into your vein (by intravenous infusion). ONC201 will be given orally once a week using capsules.

Both phases:

You will be told what part of the study you are participating in. If severe effects are severe, both drugs may be permanently stopped.

Treatment is for up to 12 months unless it is determined by your treatment team there may be benefit for you to continue treatment beyond 12 months.

It is possible that your CT scan may show an increase in the size of your cancer but your doctor thinks you may still benefit from treatment and that your doctor may suggest you continue on treatment until you have a follow-up CT scan. This will be discussed with you.

Once you come off treatment there will be a safety visit that will occur approximately 30 days and then again approximately 100 days after your last treatment. At this visit, your doctor will collect information on how you are feeling and any side effects you may be experiencing.

All patients who receive treatment will be followed for approximately 6 months after treatment completion, to collect information on disease status and survival.

Pre-medications: You may be pre-medicated with drugs to reduce the chance of having a reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor. If you do have a reaction to the drugs your doctor may start or change pre-medications to reduce the chance of you having another reaction.

Study Visits: You will be seen in the oncology clinic approximately every 14 days (prior to each treatment with nivolumab).

This visit will involve the following:

Clinical Exams: During this visit you will have a physical exam including vital signs and you will be asked questions about your general health and

This visit will involve the following:

- **Clinical Exams:** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests (approximately 3 tablespoons)** to determine your general health status and screen for certain diseases
- **Pharmacokinetic (PK) blood samples.** This looks at the movement and metabolism of the drug into and throughout the body. Each blood sample will be approximately 2 teaspoons.
 - **For patients on the Phase IB part of the study additional research blood tests for pharmacokinetics (metabolism of ONC201) will be drawn as follows:**
Cycles 1 & 2: Pretreatment, then 30 minutes, 2 hours, 4 hours, 6 hours, 24 hours, 48 hours, and 168 hours (7days) after the second treatment of ONC201. Day 7 to align with pre-dosing week 2. **Cycles 3-12:** Pre-treatment
- **Pharmacodynamic (PD) blood samples.** This looks at the effect of the drug on the body. Each blood sample will be approximately 2 teaspoons.
 - **All patients on this study (Phase IB and Phase II parts of this study) will have research blood tests for pharmacodynamics (effect of ONC201 on the body) as follows: cycles 1 and 2:** Pre-treatment, then at 6 hours, 2 days, 3 days, 7 days, after ONC201. Day 7 to align with pre-dosing week 2. In cycles 3-12: Pre-treatment. In patients who remain on study longer than 12 cycles, a sample will also be drawn pre-dosing day 1 of each cycle.
- **CfDNA blood samples.** This looks at the DNA fragments in the blood plasma. All patients will have blood samples drawn every 2 weeks in cycles 1-6. The first sample will be taken prior to ONC201, therefore in cycle 1 there will be 3 samples taken. Each blood sample will be approximately 2 teaspoons. In cycles 7-on and in patients who remain on study longer than 12 cycles, a sample will be drawn pre-dosing day 1 of each cycle only.
Review of your medicines
- **Safety evaluations**, which collects information on how you are feeling and any side effects you may be experiencing

Additional Testing:

- **CT Scan:** A CT scan will be performed approximately every 2 months to assess your tumor response to treatment.

Throughout the study a total of approximately 125 tablespoons of blood will be taken. As described above, this amount will be taken over the course of the trial, not all at once. The

amount may be less depending on what phase of the study you are on and how many cycles of treatment you complete.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include

- The drugs Nivolumab and ONC201. These drugs will be provided by BMS and Oncoceutics, respectively, the makers of the drugs, at no charge and will not be billed to you or your health insurance company.
- The costs of the research biopsies (biopsy performed prior to beginning treatment, 8 weeks after starting treatment, and at tumor progression).
- Research blood tests (pharmacokinetics and pharmacodynamics and cfDNA)
- Analysis of all tissue and blood research samples collected and drawn
- EKG's

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study.

These include all study doctor visits, standard blood tests, the administration costs of the drugs Nivolumab and ONC210, drugs used to reduce side effects, doctor visits, all blood tests not outlined above, the biopsy performed prior to beginning treatment, pregnancy tests, CT scans, MRIs, and PET scans. Therefore, all of the services listed in this paragraph will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance or your insurance does not cover these services, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact your

site's Principal Investigator, <INSERT NAME AND CONTACT>

Discomforts and Risks

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Taking part in this study may lead to time away from work.

The side effects of nivolumab and ONC201 are described below. There are also some side effects which may not yet be known. It is not known if the side effects of the combination (Nivolumab and ONC201) may be worse or the same as single agent (one drug only) use.

Many side effects might go away soon after you stop taking the ONC201. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. Several clinical studies involving ONC201 are currently ongoing with more than 200 people who have received ONC201. Due to the ongoing status of these clinical programs, the safety information is incomplete.

Risk of Study Drug

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At this time, greater than 350 patients have been treated with ONC201.

As of August 31, 2020, some patients receiving ONC201 have reported side effects as described below. Although most were mild or moderate, some may be serious:

Frequent (In 100 people receiving ONC201 21 or greater may have $\geq 21\%$) adverse events (side effects) that were attributed as possibly related to ONC201 include:

- Fatigue
- Nausea
- Headache
- Vomiting

Occasional (In 100 people receiving ONC201 4 to 20 may have (4-20%)) adverse events (side effects) that were attributed as possibly related to ONC201 include:

- Gait disturbance
- Decrease in the number of a type of white blood cell (lymphocytes)
- Insomnia
- High blood sugar
- Weakness on one side of the body
- Anemia (low count of red blood cells)

Rare (In 100 people receiving ONC201, 3 or fewer may have ($\leq 3\%$)) adverse events (side effects) that were attributed as possibly related to ONC201 include:

- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Abdominal pain
- Small bowel obstruction
- Death
- Damage to multiple organs (kidneys, liver, lungs, others)
- Encephalopathy
- Pneumonia
- Bleeding
- Blood infection
- Change in thinking patterns
- Abnormal body movement
- Rash
- Bleeding in the brain or lungs
- Blood clot in the lung
- Tumor Lysis syndrome, a disease caused by cancer cells dying
- Stroke
- Trouble breathing

Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction,

you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- A rash
- Sneezing
- Itchy, runny or blocked nose (allergic rhinitis)
- Itchy, red, watering eyes (conjunctivitis)
- Chest tightness, shortness of breath and a cough
- Swollen lips, tongue, eyes or face or other areas
- A fast pulse
- Sweating
- A feeling of dread
- Swelling around the eyes and mouth
- Swelling of the throat
- Wheezing
- Having a hard time breathing
- A sudden drop in blood pressure (making you feel dizzy or lightheaded)
- Inability to breathe without assistance

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study. You should talk to your study doctor about any side effects or changes in your health that you have while taking part in the research study, whether or not you think they are related to the study drug. Adverse reactions may occur following dosing with ONC201. You will be monitored for adverse events.

At least one patient with advanced cancer who received ONC201 has experienced tumor lysis syndrome, when a large number of cancer cells die quickly and release their content into the blood, which can cause changes in laboratory levels, leading to kidney injury, heart damage, muscle weakness, and rarely seizures.

Some patients with advanced cancer who received ONC201 have died within 30 days of receiving the study drug. High doses of ONC201 in animals have caused death.

Nivolumab:

Nivolumab is an agent involved in the inhibition of “immune checkpoints,” and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving Nivolumab. In clinical trials, most side effects were reversible and managed by stopping Nivolumab temporarily, administration of corticosteroids and supportive care. While rare, immune mediated side effects may also occur after stopping Nivolumab. These are considered late onset immune mediated toxicities, which may begin even months after stopping treatment. Your doctor will closely monitor you after you stop treatment and provide supportive care as

necessary. There are also some side effects which may not yet be known. There is a small risk of death

Frequent - Greater than 10% chance this will happen

- Diarrhea
- Nausea
- Fatigue
- Rash
- Itchiness

Occasional – Between 1 and 10% chance this will happen

- Thyroid gland abnormalities. May cause fatigue, weight gain, fluid retention, sensitivity to cold & mental apathy. Can be serious or life threatening.
- Elevated blood sugar
- Bowel inflammation. This could result in severe diarrhea and may require hospitalization for treatment. Severe and prolonged diarrhea can be life-threatening.
- Inflammation or ulceration of the mouth and lining of the digestive tract
- Vomiting
- Abdominal pain
- Constipation
- Dry mouth
- Fevers
- Swelling of the face, body, arms, or legs (edema).
- Abnormally high levels of enzymes produced by the liver meaning your liver is not functioning properly. Although this is usually mild and reversible, this can be serious or life threatening.
- Reaction to the drug infusion, including flushing, shortness of breath, dizziness, chest pain, or other symptoms.
- Infections
- Blood abnormalities, including low blood phosphate, magnesium, potassium, or sodium levels. These may require repletion or correction of abnormal blood test values.
- Blood test abnormalities, including increase in lipase or amylase, which may reflect inflammation of the pancreas.
- Decreased appetite
- Joint or muscle pain or stiffness
- Tingling, burning, or numbness in hands and feet
- Headache
- Dizziness
- Kidney failure which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up

in your body. When this happens, you may need to be hospitalized or else be placed in dialysis.

- Shortness of breath
- Cough
- Loss of color (pigment) from areas of skin
- Skin reactions, including hives, redness, and dry skin. Rarely, a skin reaction may be severe and result in extensive skin blistering (Stevens Johnson syndrome). This can be a life-threatening event.
- Hair thinning or loss
- Elevated blood pressure
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.
- Muscle or joint pain

Rare – Less than 1% chance this will happen

- Changes in heart rhythm, resulting in a fast or irregular heartbeat. Certain types of irregular heartbeats can be serious or life-threatening.
- Adrenal gland abnormalities, which may cause you to feel weak.
- Pituitary gland abnormalities, which may cause headaches, change in eyesight, increased thirst, and increased frequency passing urine.
- Diabetes. This is an elevated blood sugar that can occur when your body is not able to regulate blood sugar levels normally. Elevated blood sugar levels may be life-threatening and may require hospitalization for treatment.
- Inflammation of the eyes. This may result in decreased or blurry vision.
- Inflammation of the pancreas. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.
- Inflammation of the airways. This can result in cough or shortness of breath.
- Swollen lymph nodes
- Autoimmune disorders, including Guillain-Barre syndrome, which can be associated with progressive muscle weakness or paralysis.
- Inflammation or loss of the lining of the brain and spinal cord, which may cause neurological damage including confusion, hallucinations, difficulty walking or using arms
- Myasthenia gravis, when the body's immune system attacks muscle nerve cell receptors causing weakness in the muscles. This can be severe or life-threatening.
- Abnormal brain function due to brain inflammation (encephalitis), which can be potentially life-threatening or fatal.
- Inflammation of the blood vessels, which could cause possible bleeding and/or bruising.
- Cardiac issues, including the risk of heart inflammation, or myocarditis

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Reproductive Risks From nivolumab and ONC201

Nivolumab and ONC201 may decrease sperm count. This is usually temporary but can be permanent, which would result in sterility (not being able to father a baby).

Because the drugs in this study can affect an unborn baby, you should not become pregnant

while on this study.

Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception from time of consent and for the duration of study treatment through 5 months after the last dose of study treatment (ONC201 or Nivolumab, whichever is last). The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception from time of consent and for the duration of study treatment through 7 months after the last dose of study treatment (ONC201 or Nivolumab, whichever is last). The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

Ask your study doctor for more information regarding preventing pregnancy during the study treatments.

You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

By signing this document, you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

Antiemetics (anti-nausea medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction. You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment and alter the drug dosages if necessary.

Risk of CT imaging: CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist. There is no significant risk from this amount of radiation.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Risk of Biopsy: May cause bruises, bleeding, pain, or infection.

Benefits

While it is possible that the combination of ONC201 and nivolumab may be active against your cancer, and the side effects of this combination are not too severe, this is not yet known. We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

Alternative Therapies

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment. Your doctor will discuss with you specific standard treatment options.
- Take part in another research study if there is one available.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you make the decision to withdraw from this study (stop taking study medication) for any reason, tell your doctor immediately. You will be asked to sign a form indicating whether you

give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Khaldoun Almhanna nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <INSERT CONTACT NAME OF IRB>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this

study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor;
- Doctors, nurses, laboratories and others who provide services to you in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no effect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on

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Dates: 11/04/2018, 11/11/18, 11/16/18, 11/24/18, 11/30/18, 12/2/18, 12/6/18, 12/7/18, 12/10/18, 1/8/19 BMS review, 1/9/19, 1/13/19, 1/15/19, 1/16/19, 1/17/19, 1/20/19, 1/22/19, 2/4/19, 2/19/19, 3/19/19, AM#1 7/22/19, BMS review 8/23/19, AM#2 3/3/20, BMS approved 4/1/20, Oncoceutics approved 4/24/20, AM#3 10/26/2020, BMS approved 1/5/21, Oncoceutics approved 3/30/21

<http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONATACT INFORMATION>

about your privacy rights see the <INSERT HOSPITAL NAME> which has or will be given to you.

Research authorization for use and disclosure of information.

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form. Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to Dr. Khaldoun Almhanna, MD c/o the Medical Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.

If after you have signed this form you have any questions relating to your rights, please contact
<INSERT IRB CONTACT>

Uses and releases covered by this authorization (permission)

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

- Every research site for this study, including this hospital, and including each site's research staff and medical staff
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol
- The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research:

The study sponsor: Dr. Khaldoun Almhanna and The Brown University Oncology Research Group (the group coordinating this trial) and its representatives, Bristol Myers Squibb (the makers of Nivolumab and financial supporter of this trial) and Oncoceutics, Inc (the makers of ONC201), Pathology and laboratory departments of Rhode Island Hospital and Brown University, , and other laboratories and collaborators as contracted to perform the applicable testing or assess collected samples

- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights
- The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study

- Principal Investigator and other Investigators
- Study Coordinator
- Additional members of the Research Team
- The Patient Advocate or Research Volunteer Protector: _____
- Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
- Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)

- Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee

- The members and staff of the hospital's affiliated Privacy Board (if such a board is used)
- Others: _____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

- The entire research record and any medical records held by the hospital may be used and

released.

The following information: _____

GINA STATEMENT

This study involves ‘genetic testing’ as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some limitations to GINA’s protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA’s protections regarding the ultimate use to which your genetic information is put, <INSERT HOSPITAL NAME>’s privacy policies generally protect the privacy of such information and restrict its release outside of <INSERT HOSPITAL NAME>, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

Participation in Specimen Banking

You are agreeing to participate in this research study by signing this form (the “Main Study”) **tissue** samples will be collected from you, which will be referred to here as your ‘Specimen.’ In addition to being analyzed as part of the Main Study, your Specimen may be useful for future research purposes. By signing this consent form, you give permission for your Specimen to be stored in a specimen bank indefinitely, until it is no longer usable. The Specimen may also be used to create a cell line, which would also be stored for an indefinite period of time. Along with the specimens, portions of your personal health information collected as part of the Main Study will also be stored. Your Specimen and personal health information may be stored and analyzed at Lifespan; or, they may be shared with researchers at other institutions or companies that may store them and use them for their own research. It is very unlikely that any future research performed using your Specimen would benefit you directly. However, the research may provide important medical knowledge that in the future could help other patients with your medical condition or other medical problems.

At this time, we do not know what future research studies may be done using your Specimen. Such research studies may include genetic tests that would analyze your DNA, RNA or other gene products, like proteins and metabolites. These genetic tests may be done by Lifespan, or they may be done by other researchers with whom your Specimen and data have been shared. Because any genetic testing of your Specimen would be for research purposes, the results would have no clear implications for your health or medical condition, or that of your family members. Any testing results would not be made available to you or to any insurance company, your employer, your family, or any physician who treats you in the future.

There is a very remote possibility that your Specimen and some associated data may become part of a process or product that ultimately has commercial value. For instance, the Specimen could

be used to establish a cell line (a group of cells that are able to reproduce, sometimes indefinitely) that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

If you decide at some time in the future that you no longer wish your stored Specimen to be used in future studies, you have the right to request that the Specimen be withdrawn from the specimen bank. However, withdrawal cannot be guaranteed and may be impossible. For example, it is possible that the Specimen might no longer be identifiable as belonging to you, or it may have been used up, or it may already have been shared with other institutions or companies for their own research. To request withdrawal of your Specimen, please write to: Dr. Khaldoun Almhanna, MD 593 Eddy Street APC1 Providence, RI 02903.

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

The Researcher is required to provide a copy of this consent to you.

Signature of study volunteer/authorized representative _____ *Date* _____ *and Time when signed*

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

Signature of witness (required if consent is presented orally or at the request of the IRB) _____ *Date* _____

Signature of Translator _____ *Date* _____

Signature of researcher or designate _____ *Date* _____ *and Time when signed*

** If signed by agent other than study volunteer, please explain below.*

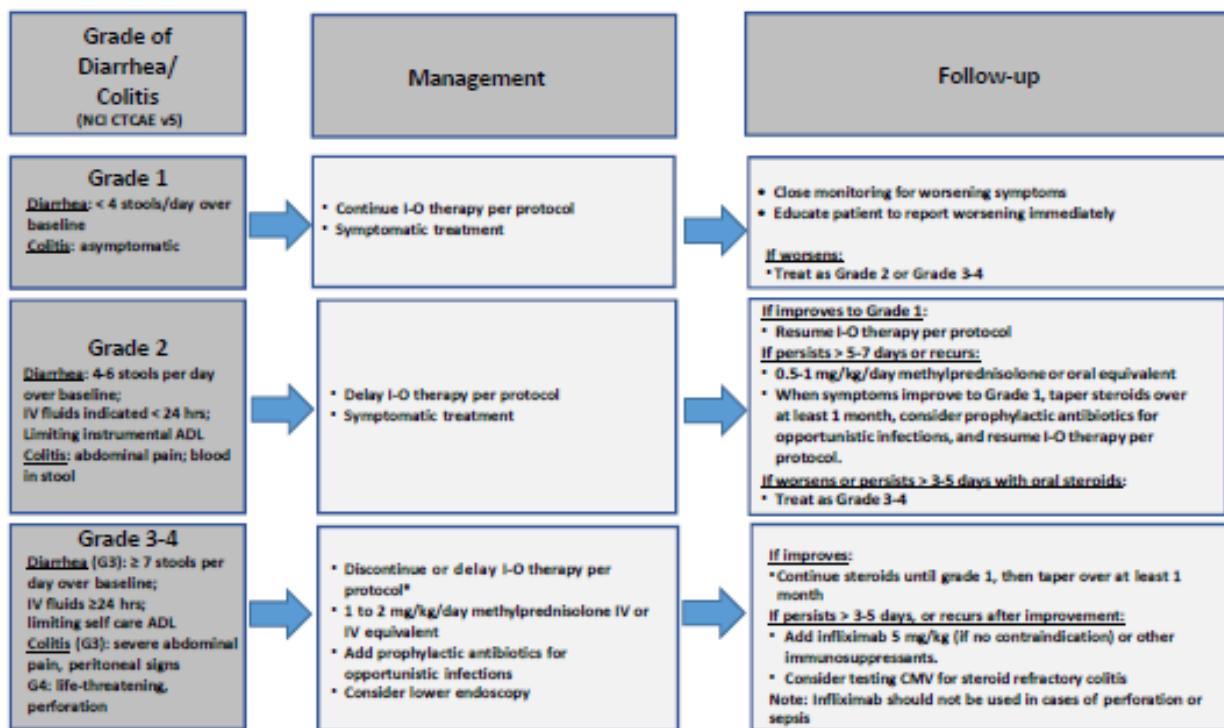
Appendix C: Performance Status

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

APPENDIX D I-O AE ALGORITHMS

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.

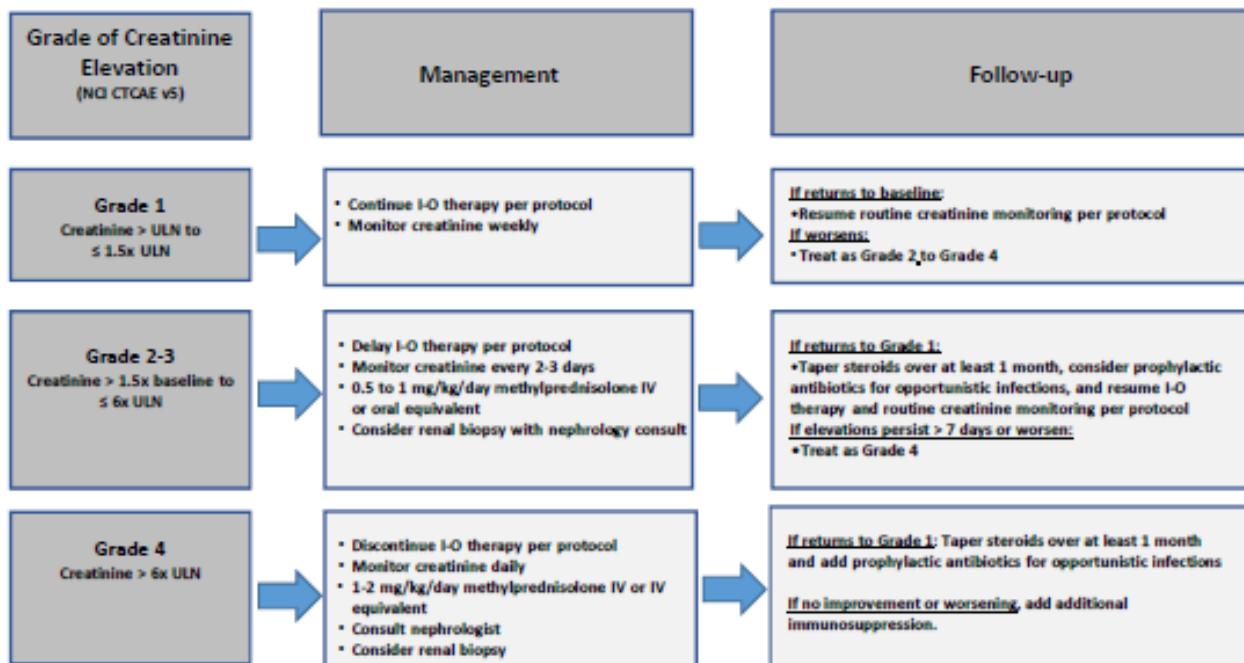


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

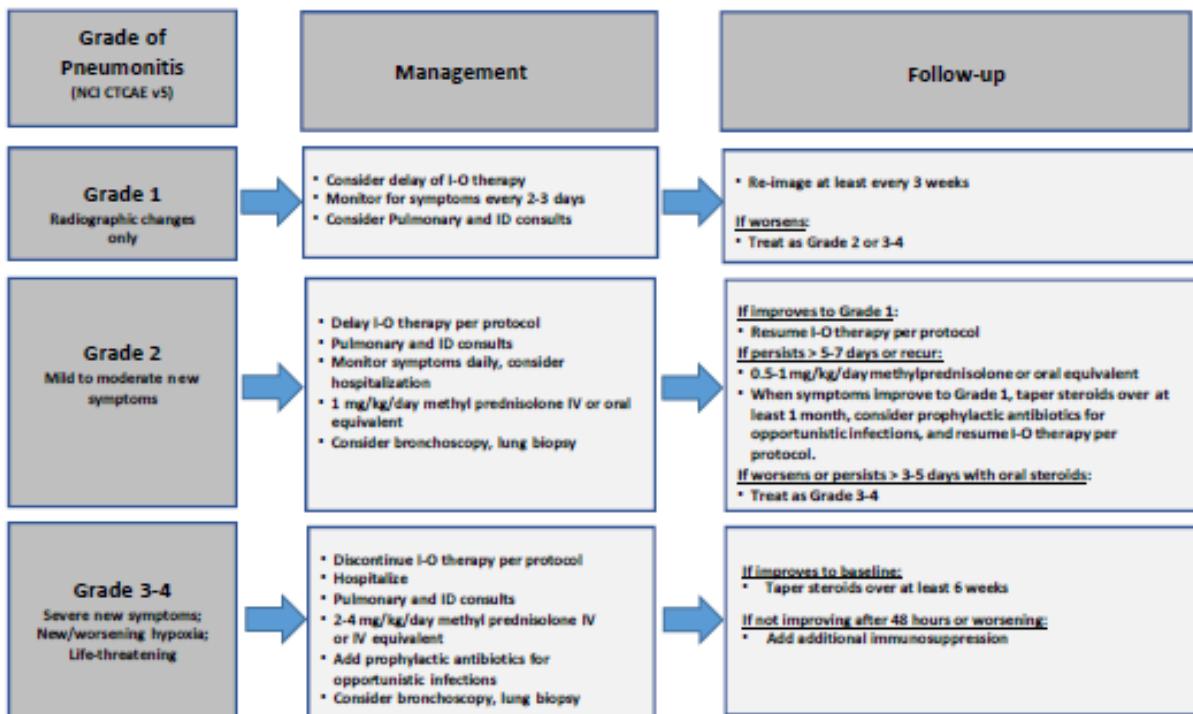
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after 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

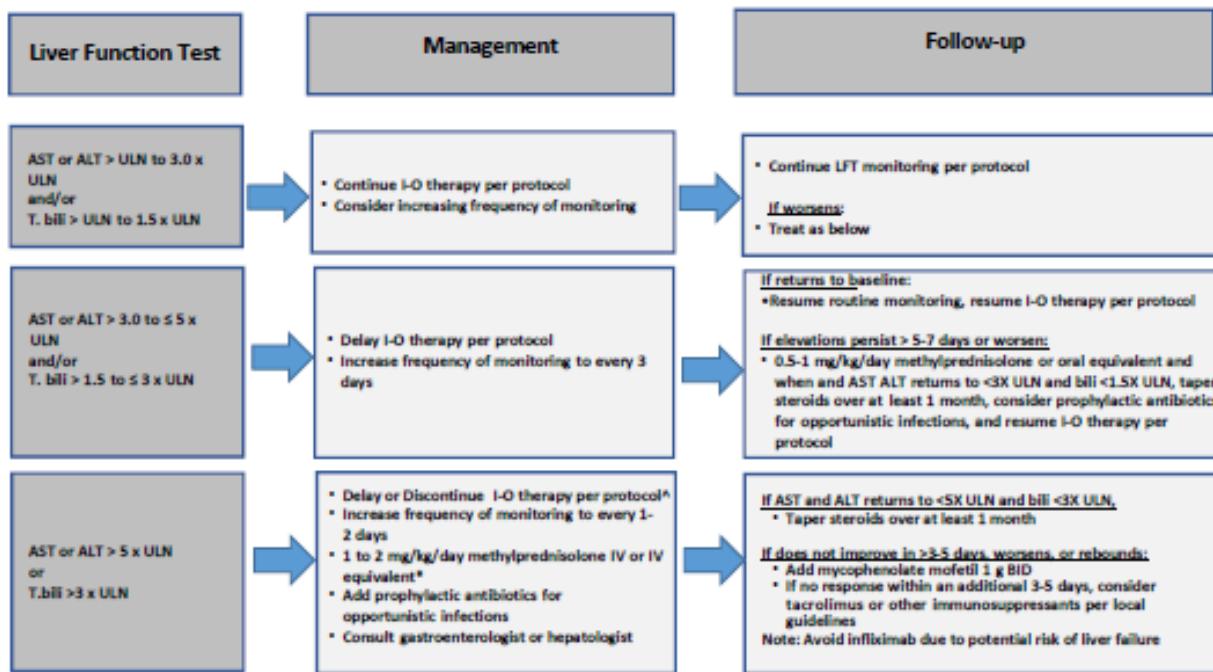
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



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

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, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

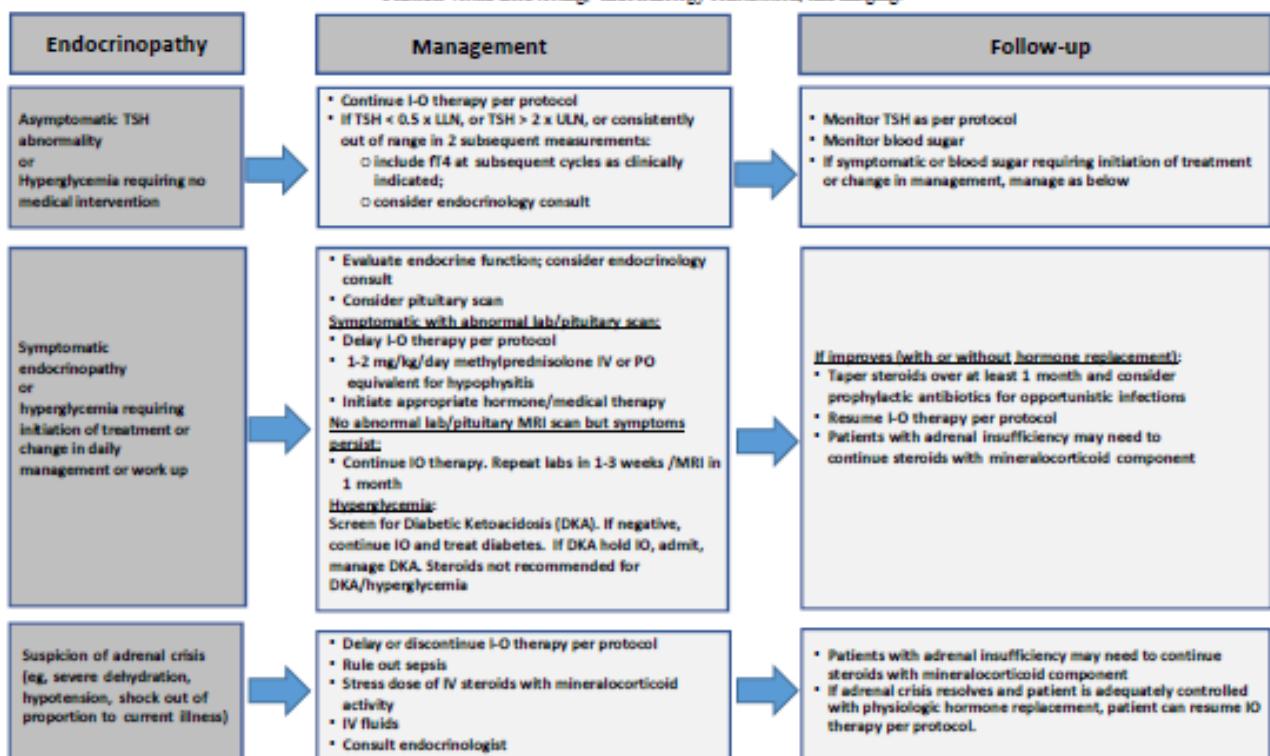
A Please refer to protocol dose delay and discontinue criteria for specific details.

*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

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

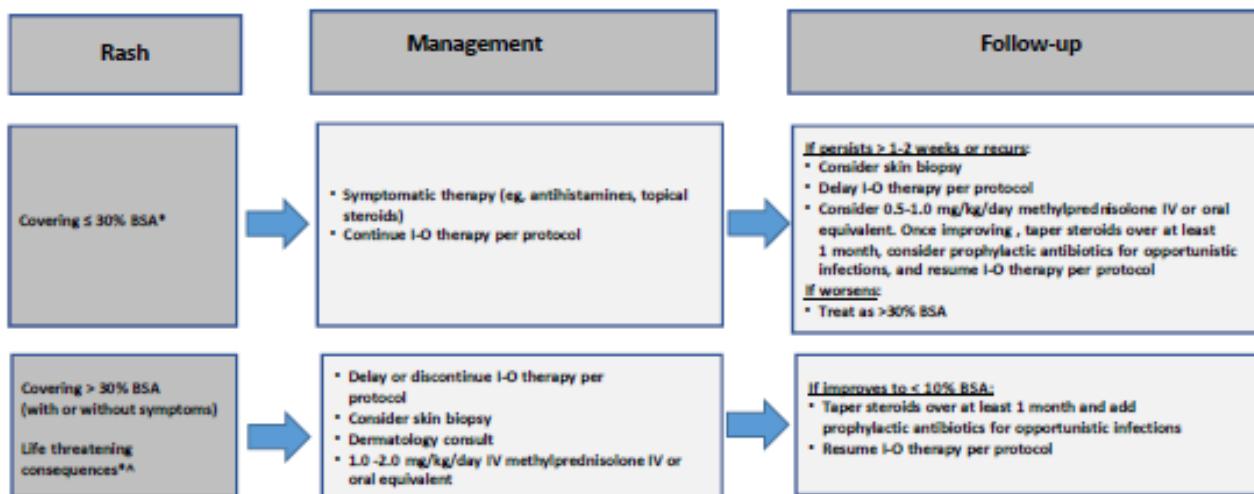
Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



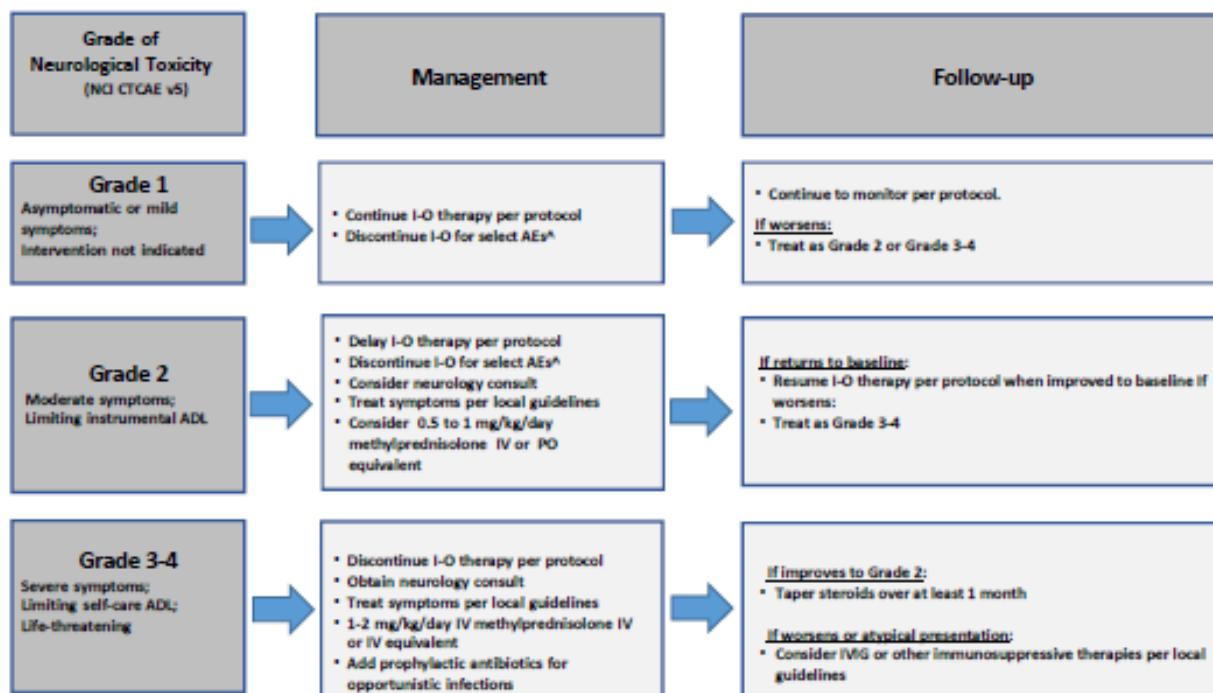
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

[^]If Steven-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS 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.

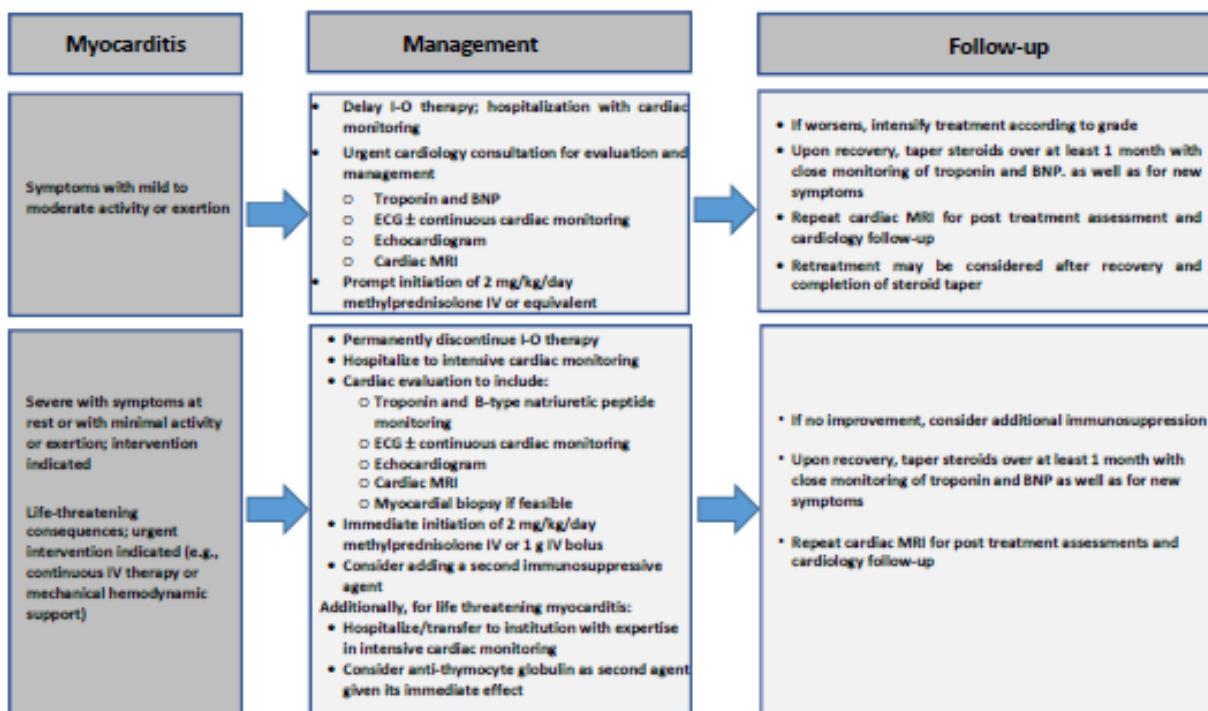


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^aDiscontinue for any grade myasthenia gravis, Guillain-Barré syndrome, treatment-related myitis, or encephalitis.

Myocarditis 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 (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

Appendix E: FDA MedWatch Reporting Checklist for site to submit with report

Patient #: _____ **Initials:** _____

Initial SAE Report Follow-up #1 SAE Report Follow-up #2 SAE Report

Report must be typed

Mfr Report #: enter the BMS Protocol # **CA209-79E**

Section A Include protocol # (and patient number, if assigned) (i.e. Br379 initials #)

Section B Description of event:

Include description of event (i.e. this is an initial SAE report to document pt X presented to the hospital on XX-XX-XXXX for X, X, X)

Include protocol description (i.e. pt X began treatment on BrUOG 379 on X)

Include treatment regimen (dosing frequency, combination therapy) (i.e. patient received last dose of X on XX-XX-XX)

Clearly outline which events are being reported as serious and non-serious (i.e. serious events are grade 3 fatigue and grade 3 nausea, non-serious events at time of hospitalization include grade 1 fever and grade 1 vomiting)

Investigator's assessment of the relationship of the serious adverse event to each investigational product (Nivolumab) and suspect medication (ONC201) (i.e. fatigue is not related to Nivolumab, related to disease)

Include documentation if the event(s) is/are immune mediated

Include treatment of event (i.e. patient received IV antibiotics and fluids for treatment of serious event X)

Outcome of event, if known (i.e. grade 3 serious fatigue resolved upon discharge or grade 3 serious fatigue downgraded to non-serious grade 2 upon discharge)

Action taken with Nivolumab and ONC201 as a result of the SAE and expectedness (based on the IB and consent) if it is unknown at the time of submission, please indicate "at this time, treating MD is uncertain when study treatment with Nivolumab and ONC201 will resume"

Create unscheduled event in REDCap and upload all supportive documents

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Dates: 11/04/2018, 11/11/18, 11/16/18, 11/24/18, 11/30/18, 12/2/18, 12/6/18, 12/7/18, 12/10/18, 1/8/19 BMS review, 1/9/19, 1/13/19, 1/15/19, 1/16/19, 1/17/19, 1/20/19, 1/22/19, 2/4/19, 2/19/19, 3/19/19, AM#1 7/22/19, BMS review 8/23/19, AM#2 3/3/20, BMS approved 4/1/20, Oncoceutics approved 4/24/20, AM#3 10/26/2020, BMS approved 1/5/21, Oncoceutics approved 3/30/21

- A final report to document discharge from hospital (or resolution of important medical event) if patient still admitted at the time of report, this must be submitted as a follow-up
- Section C Suspect Products(s)** site to complete if the initial reporter suspected the product was associated with the SAE. If the product was not suspected to be associated with the SAE, only C2 conmed section should be completed (lot # and expiration date must be included if applicable).