A Phase II Trial of Perioperative CV301 Vaccination in Combination with Nivolumab and Systemic Chemotherapy for Resectable Hepatic-Limited Metastatic Colorectal Cancer

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to the applicable institutional review board(s).

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SYNOPSIS

TITLE	A Phase II Trial of Perioperative CV301 Vaccination in Combination with Nivolumab and Systemic Chemotherapy for Resectable Hepatic-Limited Metastatic Colorectal Cancer
SHORT TITLE	Phase II trial of perioperative CV301 vaccination in combination with Nivolumab and systemic chemotherapy for CRC
PHASE	Phase II
OBJECTIVES	Primary Objective: Determine if perioperative vaccination with CV301 in combination with nivolumab, systemic chemotherapy and surgical resection improves 3 year OS as compared to perioperative nivolumab, systemic chemotherapy and surgical resection in patients with hepatic-limited metastatic colorectal cancer. Overall survival is defined as time from metastasectomy to date of death from any cause. Secondary Objectives: • Compare 3-year recurrence-free survival (RFS) between the experimental and control treatment groups. • Compare 3-year OS between the experimental and control groups • Compare OS (in the experimental and control groups) to historical controls • Evaluate the best overall response rates (both by RECIST 1.1 and surgical pathology) between the experimental and control groups. • Compare the pathologic complete response rate to neoadjuvant therapy in resected tumor tissue between the experimental and control groups. • In patients who experience a recurrence after surgery, evaluate the proportion of patients amenable to complete re-resection/ablation between the experimental and control treatment groups. • In patients who experience a recurrence after protocol therapy, compare the progression free survival post-recurrence between the experimental and control groups. • Evaluate the perioperative surgical outcomes (complications and severity scores) between the experimental and control groups. • Compare 3-year OS from the date of registration between the experimental and control Exploratory Objectives: Analyze the following laboratory experiments for biomarker analyses and correlate with response to therapy and clinical outcomes: • mRNA signature in tumor tissue pre- and post-therapy by whole transcriptome sequencing using RNAseq

	• Genomic profiling of metastatic and primary tumor DNA • CEA and MUC-1 antigen-specific immune response in pre- and post-therapy peripheral blood by intracellular cytokine staining and/or ELISPOT or other validated assays. • Other tumor-associated antigen-specific immune response measures may be assessed if adequate samples are available • TCR clonality assays • Serum cytokine, and serum soluble factors • PD-1/PD-L1 staining in pre- and post-therapy tumor tissue. • Immunoscore by IHC
STUDY DESIGN	This is a multi-center Phase II randomized study. We plan to enroll 78 patients with biopsy-proven hepatic-limited metastatic colorectal cancer deemed resectable after multi-disciplinary discussion. Eligible patients must have confirmed isolated liver metastases by radiographic imaging of the investigators' choosing. Imaging must include the chest, abdomen, and pelvis regardless of imaging modality chosen. Patients will be randomized to either the control arm or the experimental arm. The control arm will receive mFOLFOX6 every 2 weeks for 4 cycles concurrently with Nivolumab. The experimental arm will first be treated with 2 vaccinations of MVA-BN-CV301 given two weeks apart (Days -28, -14) concurrently with Nivolumab followed by 4 vaccinations of FPV-CV301 given two weeks apart concurrently with mFOLFOX6 and Nivolumab, which will again be administered every 2 weeks for 4 cycles (FPV-CV301, mFOLFOX6 and Nivolumab) After Cycle 4, patients will be re-evaluated for surgical resection by re-staging CT chest, abdomen and pelvis (C/A/P). Patients still considered resectable will undergo surgical resection with the goal of complete resection. Patients who cannot be completely resected will continue to be followed on study, and an additional appropriate candidate will be randomized to the corresponding arm. We will collect peripheral blood and tumor tissue at the time of surgical resection, if applicable, or by re-biopsy if resection is not possible. Post-operative therapy will begin when patients are deemed ready by their surgical oncologist team. Patients in the control arm will then undergo another 8 cycles of mFOLFOX6 with Nivolumab administered concurrently. Nivolumab will then be administered every four weeks. The experimental arm will receive the same post-operative regimen but including FPV-CV301 boosters given concurrently with mFOLFOX6 and Nivolumab. FPV-CV301 will then be administered every 12 weeks, and Nivolumab every 4 weeks. We will collect peripheral blood for evaluation of correlates upon the completion of therapy. The vaccination approach of initial immunization during the neoadjuvant period followed by FPV-CV301 boosters for two years postoperatively was chosen to optimize the induction of a long-lasting tumor-specific host response.

	Neoadjuvant vaccination will also allow for analysis of the tumor microenvironment in resection specimens. Post-therapy patients will be under surveillance per NCCN guidelines with repeat CEA every 3 months for 2 years followed by every 6 months for 1 year (total 3 years), repeat CT of the C/A/P every 3 months for 2 years followed by every 6 months for up to 1 year (total 3 years), and colonoscopy at one year with repetition based on findings at the time of the procedure.
KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility)	**Inclusion Criteria** 1. ECOG Performance Status of ≤ 2 and/or sufficient to undergo both perioperative systemic chemotherapy and hepatic surgery as determined by surgical and medical oncology evaluations. 2. Histologically confirmed hepatic-limited metastatic colorectal cancer. 3. Genomic testing results are required. FoundationOne platform is preferred, however results from an equivalent genomic platform may be used after discussion with the sponsor investigator. 4. Completely resectable disease as determined by the guidelines below and surgical oncology evaluation. Patients with bilobar disease that requires resection and ablation are allowed provided the surgical oncologist can render the patient NED (no evidence of disease) at the conclusion of the operation. Synchronous primary colorectal and metastatic hepatic tumors are eligible, provided all disease can be resected in a single operation. **NOTE:** Subjects who had surgery for their primary tumor prior to registration to this trial are still eligible. 5. No radiographic evidence of involvement of: extrahepatic bile ducts, main portal vein or celiac/retroperitoneal lymph nodes. 6. Adequate predicted functional liver remnant (FLR) as measured by CT and 3D CT volumetry as deemed by the individual site surgical oncologists. 7. Patients must be treatment naïve with respect to their stage IV colorectal cancer. History of prior adjuvant systemic chemotherapy containing oxaliplatin is allowed as long as it has been greater than 12 months from completion of oxaliplatin to study enrollment. **NOTE:** Neoadjuvant pelvic chemoradiotherapy as part of the management of synchronous metastatic rectal cancer is allowed, provided chemoradiation was completed prior to enrollment on study. 8. Demonstrate adequate organ function. All screening labs must be obtained within 28 days prior to registration. 9. Females of childbearing potential must have a negative serum pregnancy test within 24 hours of study drug. 10. Females of childbearing potential and males must be willing to abstain from heterosexual intercourse or to use contraception as outlined in Section 5.6

	11. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study. **Exclusion Criteria** 1. Patients with mutations in or deficient expression of one or more of the mismatch repair genes listed: MSH2, MSH3, MSH6, MLH1, PMS1, PMS2. 2. Active infection requiring systemic therapy. 3. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study). 4. Second primary malignancy within the last 2 years. Clear exceptions are 1) patient had a second primary malignancy but has been treated and disease free for at least 2 years or is considered likely to be cured by their oncologist if the period has been less than 2 years, 2) in situ carcinoma (e.g. in situ carcinoma of the cervix, basal or squamous cell skin cancer, and superficial bladder cancer). Patients with chronic lymphocytic leukemia will be allowed if their blood counts are within acceptable hematologic parameters and if they are not currently requiring cytotoxic or biologic anticancer treatment (supportive treatment such as IVIG is permitted). 5. Metastatic disease not limited to the liver. Disease not amenable to complete resection, not resectable within the confines of a single surgery, or where resection would result in inadequate functional liver remnant. 6. Has a known history of immunodeficiency including but not limited to patients with HIV/AIDS and chronic Hepatitis B/C. Testing is not required. 7. Patient with clinically significant cardiomyopathy, coronary disease, heart failure New York Heart Association (NYHA) class III or IV, or cerebrovascular accident (CVA) within 1 year of study enrollment (CV301). 8. Subjects with known severe allergy to eggs, egg products, or aminoglycoside antibiotics (for example, gentamicin or tobramycin) (CV301). 9. 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. 10. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid

	doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. 11. Participants with history of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g. Hormone replacement after adrenal crisis) 12. Patients with serious or uncontrolled medical disorders. 13. Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. 14. History of allergy or hypersensitivity to study drug components. 15. Has received a live vaccine within 30 days of the planned start of study therapy. Note: seasonal flu vaccines for injection are generally inactivated vaccines and are allowed, however intranasal influenza vaccines are live attenuated vaccines and are not allowed. 16. History of allogenic stem cell or solid organ transplant.
STATISTICAL CONSIDERATIONS	This is a phase II randomized (1:1) clinical trial comparing the control group receiving standard of care perioperative chemotherapy, nivolumab and surgery to the experimental group receiving perioperative chemotherapy, nivolumab in combination with the CV-301 vaccine. Based on a study by Morse et al.[1], the survival probability of the control group at 3 years is 0.588. With a sample size of 70 resected patients (35 per study arm), we will have 80% power to detect an increase in the 3-year OS rate from 58.8% to 88.7% using a 2.5% level one-sided log-rank test. Note that the 3-year survival rate of the vaccine treated cohort in the study by Morse et. al. was 92.5%. We will enroll 74 patients, with the expectation that about 5% of the patients will not go on to resection due to either disease progression or complications of neoadjuvant therapy [2], leaving us with approximately 70 resectable patients. If the number of unresectable patients is higher than 5%, then we will enroll up to 78 patients. An analysis is planned at 2.5 years. The purpose of this analysis is allow an early assessment of efficacy.
TOTAL NUMBER OF SUBJECTS	N = 78 patients
ESTIMATED ENROLLMENT PERIOD	Estimated 12 months

ESTIMATED STUDY DURATION	Estimated 60 months

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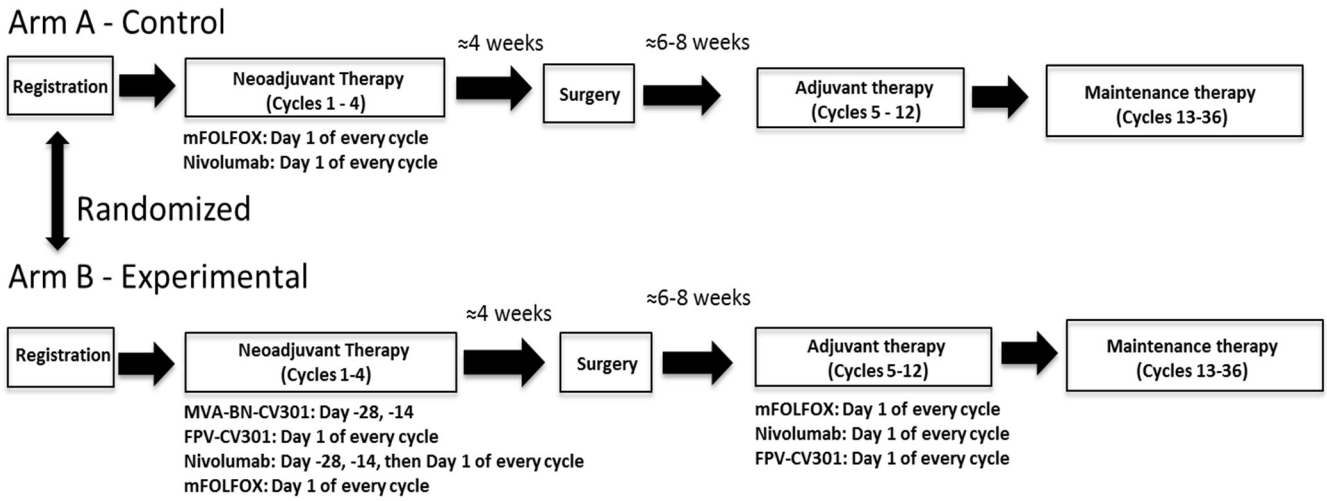
List of Abbreviations

5FU	Fluorouracil
AE	Adverse Event
ANC	Absolute Neutrophil Count
BN	Bavarian Nordic
BMS	Bristol Myers Squibb
BUN	Blood urea nitrogen
BRS	Biospecimen Repository Service
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CINJOG	Cancer Institute of New Jersey Oncology Group
CT	Computer Tomography
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
FLR	Functional Liver Remnant
FDA	Food and Drug Administration
FNA	Fine Needle Aspirate
FPV	Fowl Pox Virus
HHS	Department of Health and Human Services
ICAM-1	Intercellular Adhesion Molecule-1
IHC	Immunohistochemistry
IRB	Institutional Review Board
kg	Kilograms
LFA-3	Leukocyte Function-Associated Antigen-3
mL	Milliliters
mcg/µg	Micrograms
MRI	Magnetic Resonance Imaging
MUC1	Mucin 1
MVA	Modified Vaccinia Ankara
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PD	Progressive Disease
PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigator
PR	Partial Response
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious Adverse Event

SD	Stable Disease
sCr	Serum Creatinine
TAA	Tumor-Associated Antigens
TRICOM	TRIad of COstimulatory Molecules
ULN	Upper Limit of Normal

SCHEMA


Arm A - Control
Registration
Neoadjuvant Therapy (Cycles 1 - 4)
mFOLFOX: Day 1 of every cycle
Nivolumab: Day 1 of every cycle
≈4 weeks
Surgery
≈6-8 weeks
Adjuvant therapy (Cycles 5 - 12)
Maintenance therapy (Cycles 13-36)
Randomized
Arm B - Experimental
Registration
Neoadjuvant Therapy (Cycles 1-4)
MVA-BN-CV301: Day -28, -14
FPV-CV301: Day 1 of every cycle
Nivolumab: Day -28, -14, then Day 1 of every cycle
mFOLFOX: Day 1 of every cycle
≈4 weeks
Surgery
≈6-8 weeks
Adjuvant therapy (Cycles 5-12)
mFOLFOX: Day 1 of every cycle
Nivolumab: Day 1 of every cycle
FPV-CV301: Day 1 of every cycle
Maintenance therapy (Cycles 13-36)

1. BACKGROUND AND RATIONALE

1.1 Disease Background and Significance

Colorectal cancer remains the third most frequent cancer in both males and females, with approximately 142,000 cases reported in the United States in 2013[2]. Approximately 50% of these patients will go on to develop metastatic disease, with the liver being the most frequent, and often only site of metastatic spread. Surgical resection is the only potentially curative therapy in these patients, however, recurrence following hepatectomy occurs in approximately 75% of cases[3,4]. Due to the high frequency of recurrence, it has long been hypothesized that adjuvant systemic chemotherapy would have a role in this setting. In 2008 the results of a large, multi-center phase III randomized trial (EORTC Intergroup 40983) in which patients were randomized to FOLFOX4 administered perioperatively versus surgery alone were reported[3]. This study found that among resected eligible patients there was a 9.2% increase in progression-free survival in patients treated with perioperative FOLFOX (p=0.025), thus allowing the authors to conclude that perioperative chemotherapy has a benefit in these patients. However, a recent follow-up publication from this trial indicated that at a median follow-up of 8.5 years there was no statistically significant improvement in OS[5]. While it is felt by the oncology community that this trial was underpowered and therefore unable to demonstrate a significant improvement in OS (presumably when one indeed exists), nonetheless, it emphasizes the need for novel adjuvant trials in patients with resectable hepatic colorectal metastases[6].

One such novel approach to the treatment of metastatic colorectal cancer is to use an immunotherapeutic strategy to stimulate the immune system's recognition and destruction of cancer cells. Multiple studies in primary colorectal cancer investigating the relationship between the tumor immune microenvironment and outcome have concluded that the immune cell type and density as well as the transcriptome, correlate with relapse-free and OS, and are equivalent if not superior in prognostic value to histopathologic staging[7-9]. More recently similar results have been found in studies focusing on patients undergoing surgery for hepatic colorectal metastases[10-12].

Therapeutic cancer vaccines represent a promising avenue in immunotherapy for multiple solid organ cancers. Considerable pre-clinical and clinical data has been generated using vector-based vaccines expressing tumor antigens, particularly Carcinoembryonic (CEA) and Mucin 1 (MUC1) antigens, indicating that these vaccines are safe and capable of eliciting anti-tumor immune responses[13-16]. In an effort to elicit additive or synergistic immune responses, a vaccine that expresses both CEA and MUC1, as well as several co-stimulatory molecules (PANVAC), was engineered into recombinant vaccinia (PANVAC-V) as a priming vaccination and fowlpox (PANVAC-F) as a multiple booster vaccination.

In a pilot study, PANVAC was evaluated in 25 patients with chemorefractory, metastatic gastrointestinal (esophageal, gastric, pancreatic, colorectal), breast, ovarian and lung cancers where it was found to be safe and demonstrated immune and clinical responses[16]. The safety and tolerability, as well as further evidence of clinical benefit of this vaccine approach, were reported in a second pilot study of 26 patients with chemorefractory metastatic breast and ovarian cancer[17]. In an effort to evaluate PANVAC in a more limited disease setting, PANVAC was studied in a multicenter trial of patients with resected hepatic colorectal metastases. The purpose

of this trial was to compare two methods of PANVAC vaccination for efficacy using recurrence-free (RFS) and OS as endpoints. The two methods were prime-boost immunization with dendritic cells modified ex-vivo with PANVAC versus PANVAC administered subcutaneously[1]. Patients with liver and lung metastases (the majority had liver) that had undergone complete resection and had received at minimum 2 months of perioperative chemotherapy were eligible. Patients in the dendritic cell/PANVAC-V arm (DC/PANVAC-V) received one dose followed by three doses of the DC/PANVAC-F at monthly intervals. The second arm received a onetime PANVAC-V priming dose followed by 3 doses of PANVAC-F at monthly intervals. Both arms received doses of GM-CSF subcutaneously for four days at the injection sites after each vaccination. Two-year (RFS and OS were the clinical endpoints measured. Interestingly, there was not a statistically significant difference in RFS or OS when comparing the two arms of the study. However, when the two vaccination arms were combined and compared to a contemporary control cohort of unvaccinated patients there was a significant difference in OS in favor of the vaccinated patients, with the median OS of the contemporary cohort at 44.1 months while that of the vaccinated group had not been reached. Importantly, the RFS between the two groups was not significantly different, indicating the importance of further trials to better characterize the effect of PANVAC in this patient population, with the use of OS as the preferred clinical endpoint. While this difference in survival was remarkable, the trial has been criticized because the control group and the vaccinated groups were not randomized. Thus, in order for PANVAC to move forward into phase III testing, this result will need to be validated with a randomized control group treated with standard of care multimodality therapy.

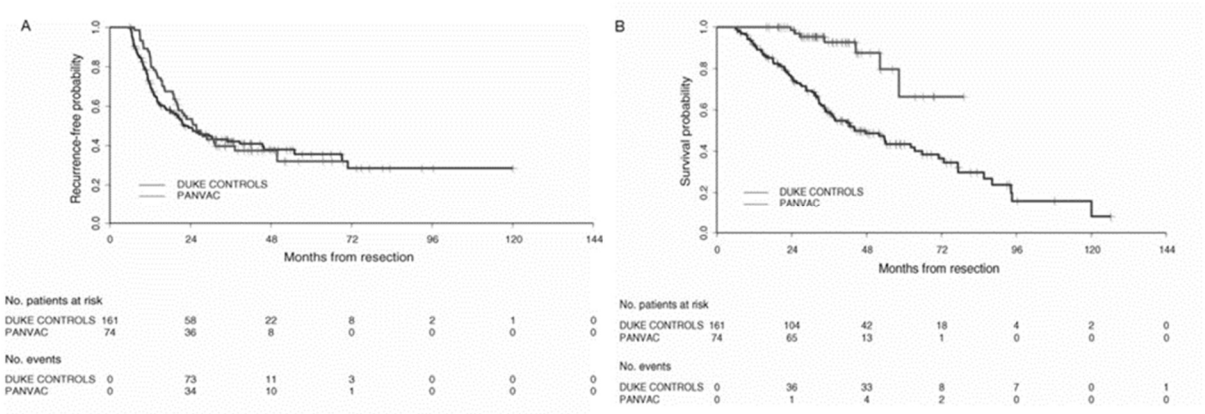


Figure 1. A) Recurrence-free survival for vaccinated patients combined versus contemporary, unvaccinated controls. RFS was measured from the date of metastasectomy until documented disease recurrence at any site. Median RFS (95% CI) was 21.9 (16.9-38.8) and 25.7 (20.0-37.2), months, respectively. B) OS for vaccinated patients combined compared with contemporary, unvaccinated controls. OS was measured from metastasectomy until death from any cause. Patients were censored on the date of last known follow-up. Median OS (95% CI) was not reached and 44.2 (36.2-63.4), months, respectively[1]. *95% CI indicates 95% confidence interval

Further clinical evidence in support of the use of PANVAC in gastrointestinal cancers comes from our group. In a first-in-man Phase I study, patients with adenocarcinoma of the pancreas were treated using a combination of EUS-guided intrapancreatic tumor injection and systemic boost using PANVAC-F and PANVAC-V. The study represents the translation of our unique

demonstration in murine models of bladder[18] and orthotopic mammary tumors[19] that tumor anergy to systemic immunization could be overcome by immunization into the tumor microenvironment using antigen-encoding vaccinia recombinants. Consented patients with locally advanced or minimally metastatic pancreatic cancer received EUS-guided intrapancreatic injections (IT) of recombinant PANVAC-F (Fowlpox encoding MUC-1, CEA, TRICOM), systemic subcutaneous (SC) PANVAC-V (vaccinia) and SC PANVAC-F boosts. Systemic SC vaccines were accompanied by subcutaneous rH-GM-CSF, 100 mcg X 4 days. Patients received 2 intrapancreatic injections of PANVAC-F (2 weeks apart) with systemic PANVAC-V and PANVAC-F boosts given with GM-CSF extending to day 71 (total of 2 IT PANVAC-F, 1 SC PANVAC-V, 4 SC PANVAC-F). Patients were allowed to transition to standard care at day 31. Patients were evaluated for toxicity and tumor progression. In this dose escalation study, the first cohort of 6 patients received IT PANVAC-F (108 PFU), SC PANVAC-V (2 X 108), and SC PANVAC-F (109). The second dose cohort of 8 pts received IT PANVAC-F (109 PFU), SC PANVAC-V (2 X 108), and SC PANVAC-F (109). At dose level 1, two of six patients were removed from study after approximately two weeks due to rapid disease progression and died one and six months after trial initiation respectively. At dose level 2, one patient was removed due to rapidly progressive disease and died at 1 month, and a second patient withdrew following 1 IT inoculation and died at month 16. Of the remaining 10 pts, 3 presented with distant metastatic disease (median survival 7 mos, range 1-25) and 7 presented without distant metastases (median survival 16 mos, range 3-35). Of note, none of the 7 patients presenting without metastatic disease developed distant visceral metastases by imaging available to us but died of sequelae associated with progressive localized disease. Of the above 10 pts, all but one transitioned initially to treatment with gemcitabine-based therapy (the remaining patient did not begin systemic treatment). Initial RNAseq transcriptome analysis comparing Day 1 and Day 14 fine needle aspirate (FNA) samples demonstrated a significant increase in a series of chemokines associated with the induction of an immune response in the tumor microenvironment. A planned series of immunologic and genetic analyses are underway. The results demonstrate that the "first in man" intra-pancreatic administration of recombinant poxvirus was well tolerated with the complete regimen suggesting an encouraging period of stable disease. The finding that none of the patients who presented without distant visceral metastases developed such, is thought to be due to the generation of a systemic immune response with effects on seeded metastatic cells. Analysis of local and systemic immune responses is currently proceeding and we hope will provide further insights.

Nevertheless, it is important to consider that, when dealing with immunotherapy, the tumor microenvironment determines whether a patient can make an effective immune response to his/her tumor. Tumor cells can induce an immunosuppressive milieu through multiple tolerogenic factors and expression of inhibitory surface receptors that create a shield around the tumor, resulting in evasion of the immune response. Two such mechanisms include (a) expression of PD-L1 in tumor or infiltrating cells, which triggers PD-1 on T-cells, inhibiting T-cell activation and expansion of previously activated T-cells; and (b) recruitment of T-regulatory cells, which are thought to suppress antitumor immune responses, into the tumor.

Although clinical evidence may support the use of CV301 (next generation PANVAC), pre-clinical data have shown that a similar antigen expressing poxvirus vaccine is able to up-regulate levels of PD-L1 in the tumor microenvironment, thus preventing the immune system from killing

cancer cells. This suggests that a combination of CV301 with anti-PD-1 therapy might be a more efficacious addition to cytotoxic chemotherapy than either CV301 or a checkpoint inhibitor alone.

The antibody-drug known as Nivolumab, binds to PD-1 with high affinity inhibiting the binding of PD-1 to its ligands PD-L1 and PD-L2. In the clinic, Nivolumab has been investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies for the treatment of several types of cancer. Most studies are still ongoing and, as such, the safety profile of Nivolumab combinations continues to evolve. Nevertheless, in association with chemotherapy (platinum-based) the safety profile of Nivolumab appeared manageable and consistent with that reported for the monotherapy regiment, with no safety concerns identified[20]. Furthermore, in the currently ongoing trial CV301-2015-201 (NCT02840994), three patients have been exposed to administrations CV301 (MVA/FPV) plus several doses of Nivolumab (13, 8 and 2 doses respectively). No SAEs, adverse events of special interest or dose-limiting toxicities have been observed to date (as of 09-Apr-2018). Also, no immune-mediated adverse events of special interest have been reported from this cohort.
In this study, we aim to determine if perioperative vaccination with CV301 in combination with Nivolumab and perioperative systemic chemotherapy improves OS as compared to Nivolumab plus perioperative chemotherapy in patients undergoing surgical resection of hepatic-limited metastatic colorectal cancer.

1.2 Clinical Profile of MVA-BN and Recombinant MVA-based Vaccines

MVA-BN Vector Backbone

CV301 is a next-generation product based on the same antigen inserts as PANVAC, but using the non-replicating MVA-BN vector as priming component instead of PANVAC's replicating vaccinia vector.

To date, 22 clinical trials evaluating the safety and immunogenicity of MVA-BN have been completed and one clinical trial is ongoing. Currently, more than 8,800 subjects have been exposed to MVA-BN including risk groups with contraindications to conventional smallpox vaccines. Furthermore, BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines (including MVA-BN-Filo) in healthy subjects, HIV infected individuals, populations with cancer and children. In total, for MVA-BN and MVA-BN-based recombinant vaccines, the exposure sums up to more than 13,300 subjects.

Furthermore, BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines in more than 900 subjects including healthy subjects, HIV infected individuals and populations with cancer and children in completed trials. In recombinant MVA vaccine trials, doses up to at least 5×10^8 $TCID_{50}$ (nominal titer) were administered applying varying schedules of repeat vaccinations, e.g. a 3-dose schedule was used for recombinant HIV vaccines and multiple vaccinations have also been performed in subjects receiving a recombinant therapeutic breast cancer vaccine (MVA-BN-HER2).

Furthermore, more than 3,600 subjects have been enrolled in completed and ongoing clinical trials with MVA-BN Filo® , ranging from Phase 1 to Phase 3 trials. The preliminary safety data are consistent with the previous experience.

.In total, for MVA-BN and MVA-BN-based recombinant vaccines, the exposure sums up to more than 13,300 subjects (more than 8,800 with MVA-BN, more than 900 with recombinant vaccines other than MVA-BN Filo, and more than 3,600 with MVA-BN-Filo). . For more details, refer to the current IB of MVA-BN-CV301 vaccine.

1.3 Safety Overview for the Combination CV301 plus Anti-PD-1 Therapy Clinical Trial CV301-2015-201

The safety and tolerability of CV301 in combination with Anti-PD1-Therapy is currently evaluated in the ongoing trial CV301-2015-201 (A Phase 1/2 Trial of CV301 in Combination with Anti-PD-1 Therapy versus Anti-PD-1 Therapy alone in Subjects with Non-Small Cell Lung Cancer, ClinicalTrials.gov Identifier: NCT02840994).

In the Phase 1 part of this trial, 12 subjects with various CEA/MUC-1 positive cancers have been enrolled, 6 male and 6 female subjects, aged between 39 and 77 years (Gatti-Mays 2019) (GATTI-MAYS, M. E., STRAUSS, J., DONAHUE, R. N., PALENA, C., DEL RIVERO, J., REDMAN, J. M., MADAN, R. A., MARTE, J. L., CORDES, L. M., LAMPING, E., ORPIA, A., BURMEISTER, A., WAGNER, E., PICO NAVARRO, C., HEERY, C. R., SCHLOM, J. & GULLEY, J. L. 2019. A Phase 1 Dose Escalation Trial of BN-CV301, a Recombinant Poxviral Vaccine Targeting MUC1 and CEA with Costimulatory Molecules. *Clin Cancer Res*).

In the ongoing Phase 1b part of the trial, 12 subjects (nine females and three males between 48 and 74 years) were enrolled: four subjects in cohort 1 received up to 15 doses of combination of CV301 and nivolumab over a period of up to approximately 16 months. In cohort 2, eight subjects received up to nine doses combination of CV301 and pembrolizumab over a period of up to nine months.

1.3.1 Serious Adverse Events

One unexpected related SAE case was classified as a dose limiting toxicity (DLT) during combination treatment of CV301 and nivolumab. The subject had started treatment on 28-MAR-2018. During administration of the 2nd dose of nivolumab on 11-APR-2018, the infusion was interrupted due to infusion reaction. On 25-APR-2018, she complained of continuing cough and dyspnea, CT scan was indicative of pneumonitis, and the patient was started on prednisone. On 21-MAY-2018 she was hospitalized for management of ongoing shortness of breath due to pneumonitis grade 3 (meeting seriousness criteria). On 25-MAY-2018 there was onset of disseminated intravascular coagulation (DIC) while hospitalized, on 26-MAY-2018 she was diagnosed with vasculitis while hospitalized. The patient died on 31-MAY-2018 due to multi-organ failure. This case was discussed in the safety management team. The relationship was most probably to the anti-PD1 treatment, as such events are known reactions for immune checkpoint inhibitors, but for the pneumonitis also possibly related to CV301.

Furthermore, four other subjects reported eight SAEs unrelated or unlikely related to CV301 (autoimmune hepatitis with liver enzyme elevations, obstructive pneumonia; intracranial vascular stroke; dysarthria and memory impairment).

1.3.2 Clinical Trial CV301-BLD-001

This is an ongoing, BN-sponsored Phase 2, multicenter, single-arm trial of CV301 in combination with PD-1/L1 blockade in patients with locally advanced or metastatic urothelial bladder cancer (ClinicalTrials.gov Identifier: NCT02840994).

As of June 30th, 2019, 37 patients were dosed with CV301 in combination with atezolizumab. Data is still preliminary.

1.3.3 Clinical Trial 2017-1189 / BN-IST-017

This is an ongoing, Investigator-sponsored Phase 1/2, multicenter, open label, randomized, one-arm trial of CV301 with PD-1/L1 blockade in patients with hepatic-limited metastatic colorectal cancer or pancreatic adenocarcinoma (ClinicalTrials.gov Identifier: NCT03628716).

As of June 30th, 2019, six patients were enrolled and dosed with CV301 in combination with durvalumab. Data is still preliminary.

The overall frequency of immune mediated events under combination treatment of CV301 plus anti-PD1 seems to be in line with previously published experience for anti-PD1 alone (Brahmer, 2018) (Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA. (2018).Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018; 36:1714-1768).

2. STUDY OBJECTIVES

2.1 Primary Objective

Determine if perioperative vaccination with CV301 in combination with nivolumab, systemic chemotherapy and surgical resection improves 3 year OS as compared to perioperative nivolumab, systemic chemotherapy and surgical resection in patients with hepatic-limited metastatic colorectal cancer. Overall survival is defined as time from metastasectomy to date of death from any cause.

2.2 Secondary Objectives

- Compare 3- year recurrence-free survival (RFS) between the experimental and control treatment groups.
- Compare 3-year OS between the experimental and control groups
- Compare OS (in both the experimental and control groups) to historical controls
- Evaluate the best overall response rates (both by RECIST 1.1 and surgical pathology) between the experimental and control groups.

- Compare the pathologic complete response rate to neoadjuvant therapy in resected tumor tissue between the experimental and control groups.
- In patients who experience a recurrence after surgery, evaluate the proportion of patients amenable to complete re-resection/ablation between the experimental and control treatment groups.
- In patients who experience a recurrence after protocol therapy, compare the progression free survival post-recurrence between the experimental and control groups.
- Evaluate the perioperative surgical outcomes (complications and severity scores) between the experimental and control groups.
- Compare 3-year OS from the date of registration between experimental and control groups

2.3 Correlative/Exploratory Objectives

Analyze the following laboratory experiments for biomarker analyses and correlate with response to therapy and clinical outcomes:

- mRNA signature in tumor tissue pre- and post-therapy by whole transcriptome sequencing using RNAseq
- Genomic profiling of metastatic and primary tumor DNA
- CEA and MUC-1 antigen-specific immune response in pre- and post-therapy peripheral blood by intracellular cytokine staining and/or ELISPOT or other validated assays.
- Other tumor-associated antigen-specific immune response measures may be assessed if adequate samples are available
- TCR clonality assays
- Serum cytokine, and serum soluble factors
- PD-1/PD-L1 staining in pre- and post-therapy tumor tissue.
- Immunoscore by IHC

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subjects must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of ≤ 2 and/or sufficient to undergo both perioperative systemic chemotherapy and hepatic surgery as determined by surgical and medical oncology evaluations.

4. Histologically confirmed hepatic-limited metastatic colorectal cancer.

5. Genomic testing results are required. FoundationOne platform is preferred, however results from an equivalent genomic platform may be used after discussion with the sponsor investigator.

6. Completely resectable disease as determined by the guidelines below and surgical oncology evaluation. Patients with bilobar disease that requires resection and ablation are allowed provided the surgical oncologist can render the patient NED (no evidence of disease) at the conclusion of the operation. Synchronous primary colorectal and metastatic hepatic tumors are eligible, provided all disease can be resected in a single operation. **NOTE:** Subjects who had surgery for their primary tumor prior to registration to this trial are still eligible. Additionally:
   - No radiographic evidence of involvement of: extrahepatic bile ducts, main portal vein or celiac/retroperitoneal lymph nodes.
   - Adequate predicted functional liver remnant (FLR) as deemed by the individual site surgical oncologist.

7. Patients must be treatment naïve with respect to their stage IV colorectal cancer. History of prior adjuvant systemic chemotherapy containing oxaliplatin is allowed as long as as it has been greater than 12 months from completion of oxaliplatin to study enrollment. **NOTE:** Neoadjuvant pelvic chemoradiotherapy as part of the management of synchronous metastatic rectal cancer is allowed, provided chemoradiation was completed prior to enrollment on study.

8. Demonstrate adequate organ function as defined in the table below. All screening labs must be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Platelet Count	≥ 100,000 mm^3
Absolute Neutrophil Count (ANC)	≥1500 μ/L
Hemoglobin (Hgb)	≥ 9 g/dL
Renal	
Creatinine OR Calculated Creatinine Clearance[1]	< 1.5x ULN OR ≥ 60 mL/min for participants with creatinine levels > 1.5x ULN
Hepatic	
Total Bilirubin	≤ 1.5 × upper limit of normal (ULN)[2]
Aspartate aminotransferase (AST)	≤ 5 × ULN; given presence of liver metastases
Alanine aminotransferase (ALT)	≤ 5 × ULN; given presence of liver metastases
Alkaline Phosphatase	< 2.5 x ULN
Coagulation	
International Normalized Ratio (INR) or prothrombin time (PT) or activated partial thromboplastin time (aPTT)	≤ 1.5x ULN unless participant is receiving anticoagulant therapy, in which case they must be on a stable dose

[1]Cockcroft-Gault formula will be used to calculate creatinine clearance
[2]If patient has conditions of congenital hyperbilirubinemia, then patient must have isolated hyperbilirubinemia (e.g. no other liver function test abnormalities) with maximum bilirubin < 2 x institutional ULN

9. Females of childbearing potential must have a negative serum pregnancy test within 24 hours of study drug. **NOTE:** Females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months without another cause, or a documented serum follicle stimulating hormone (FSH) ≥ 35 mIU/mL. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

10. Females of childbearing potential and male participants must be willing to abstain from heterosexual intercourse or to use contraception as outlined in Section 5.6.

11. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.2 Exclusion Criteria

1. Patients with mutations in or deficient expression of one or more of the mismatch repair genes listed: MSH2, MSH3, MSH6, MLH1, PMS1, PMS2.

2. Active infection requiring systemic therapy.

3. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

4. Second primary malignancy within the last 2 years. Clear exceptions are 1) patient had a second primary malignancy but has been treated and disease free for at least 2 years or is considered likely to be cured by their oncologist if the period has been less than 2 years, 2) in situ carcinoma (e.g. in situ carcinoma of the cervix, basal or squamous cell skin cancer, and superficial bladder cancer). Patients with chronic lymphocytic leukemia will be allowed if their blood counts are within acceptable hematologic parameters and if they are not currently requiring cytotoxic or biologic anticancer treatment (supportive treatment such as IVIG is permitted).

5. Metastatic disease not limited to the liver.

6. Disease not amenable to complete resection, not resectable within the confines of a single surgery, or where resection would result in inadequate functional liver remnant.

7. Has a known history of immunodeficiency including but not limited to patients with HIV/AIDS and chronic Hepatitis B/C. Testing is not required.

8. Patient with clinically significant cardiomyopathy, coronary disease, heart failure New York Heart Association (NYHA) class III or IV, or cerebrovascular accident (CVA) within 1 year of study enrollment (CV301).

9. Subjects with known severe allergy to eggs, egg products, or aminoglycoside antibiotics (for example, gentamicin or tobramycin) (CV301).

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 start of study 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. Participants with history of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g. Hormone replacement after adrenal crisis)

13. Patients with serious or uncontrolled medical disorders.

14. Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

15. History of allergy or hypersensitivity to study drug components.

16. Has received a live vaccine within 30 days of the planned start of study therapy. **NOTE:** seasonal flu vaccines for injection are generally inactivated vaccines and are allowed, however intranasal influenza vaccines are live attenuated vaccines and are not allowed.

17. History of allogenic stem cell or solid organ transplant.

4. SUBJECT REGISTRATION

This protocol is open to both men and women and all races. All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered and randomized prior to starting protocol therapy. Subjects must begin therapy **within 5 business days** of randomization.

4.1 Randomization

1:1 randomization with no stratification.

5. TREATMENT PLAN

The experimental aspect of this protocol is in the use of perioperative CV301 in combination with Nivolumab plus mFOLFOX6 in patients with hepatic-limited metastatic colorectal cancer. mFOLFOX6 is an FDA-approved regimen for perioperative use in patients undergoing surgery for hepatic-limited metastatic colorectal cancer. Nivolumab is a human programmed death receptor-1 (PD-1) blocking antibody approved by the FDA for the treatment of several cancer types. The safety and optimal dosing of PANVAC were established in several tumor types[13-17]. The safety and optimal dosing of CV301 (formally known as PANVAC) has been established in a recent phase I/II clinical trial.

5.1 Sequence of Treatment

5.1.1 Prior to neoadjuvant therapy

Eligible patients must have biopsy-proven isolated liver metastases by radiographic imaging of the investigators' choosing and deemed resectable after multi-disciplinary discussion. After providing informed consent patients will undergo a core biopsy of tumor tissue from the metastatic site for correlative studies. If the patient has already had a prior fine needle biopsy, they will need to undergo a repeat biopsy (core biopsy) to obtain the necessary tissue for correlative studies. We will also collect peripheral blood for both, baseline lab work as well as for the planned correlates. Tissue samples will be reviewed for confirmation of diagnosis and used for molecular studies as described.

5.1.2 Neoadjuvant Therapy

Patients who are eligible for and consent to enroll onto this trial will be randomized to either the control arm or the experimental arm. One cycle is 2 weeks.

- Patients in the control arm (Arm A) will receive mFOLFOX6 and Nivolumab given on Day 1 of every 2 week cycle for 4 cycles (Cycle 1 - Cycle 4). The treatment order for Arm A is Nivolumab followed by mFOLFOX6.
- The experimental arm (Arm B) will receive two doses of Nivolumab and MVA-CV301 each given Days -28, -14, followed by four cycles of Nivolumab plus FPV-CV301 given on Day 1 of every 2 week cycle concurrently with mFOLFOX6, which will again be administered every 2 weeks for 4 cycles (Cycle 1 – Cycle 4). For Arm B the order of administration is Nivolumab followed by the vaccination at least one hour prior to mFOLFOX6.

A window of +2 days between administration of Nivolumab +/- vaccination and mFOLFOX6 is allowed. This window will accommodate subjects that receive their chemotherapy locally. If there is more than a 2-day delay for any reason, administration of study drugs should be re-aligned so that the chemotherapy falls within +2 days with the next cycle.

5.1.3 Surgical Resection

About 2 weeks after neoadjuvant therapy, patients will be re-evaluated for surgical resection with re-staging imaging of the C/A/P. Patients still considered resectable will undergo surgical resection about 4 weeks after completion of neoadjuvant therapy. The goal of surgical resection is completely treating all of their disease by either resection and/or ablation. Patients with bilobar disease must have all of their disease treated in a single operation. Synchronous primary

colorectal and metastatic hepatic tumors are eligible, provided all disease can be resected in a single operation. We will collect peripheral blood and tumor tissue at the time of surgical resection, if applicable, or by re-biopsy if resection is not possible.

Patients deemed unresectable will be managed according to their individual cancer center's disease group management team and will continue to receive Nivolumab (Arm A and Arm B) +/- vaccine (Arm B) as described below. There is no delay required to proceed with study treatment.

In the event that administration of nivolumab +/- the vaccine is impacting the delivery or tolerability of standard of care therapy, patients will be removed from protocol therapy but will continue to be followed on study.

5.1.4 Adjuvant Therapy

Once patients in the post-operative period are deemed ready to begin therapy (about 6-8 weeks after surgery) or for those subjects that are deemed unresectable and continue with treatment:

- Patients in the control arm (Arm A) will receive 8 cycles of mFOLFOX6 in addition to nivolumab given every 2 weeks through completion of chemotherapy: Cycle 5 – Cycle 12. The treatment order for Arm A is Nivolumab followed by mFOLFOX6.
- Patients in the experimental arm (Arm B) will receive 8 cycles of mFOLFOX6 in addition to nivolumab and FPV-CV301 boosters given every 2 weeks through completion of chemotherapy: Cycle 5 - Cycle 12. For Arm B the order of administration is Nivolumab followed by the vaccination at least one hour prior to mFOLFOX6.

If possible, nivolumab (Arm A and Arm B) +/- the CV301 (Arm B) will be administered on the day (+2 days) that systemic chemotherapy resumes. We will re-collect peripheral blood for evaluation of correlates per the study calendar. For Arm B the order of administration is Nivolumab followed by the vaccination at least one hour prior to mFOLFOX6. A window of +2 days between administration of Nivolumab +/- vaccination and mFOLFOX6 will be allowed. This window will accommodate subjects that receive their chemotherapy locally. If there is more than a 2-day delay for any reason, administration of study drugs should be re-aligned so that the chemotherapy falls within +2 days with the next cycle.

In the event that patients in the experimental arm suffer complications that render them unfit for adjuvant systemic chemotherapy or that they cannot complete their adjuvant systemic chemotherapy due to toxicity, patients will still be eligible to receive their scheduled nivolumab and/or CV301 provided the investigators deem them fit enough to do so.

5.1.5 Maintenance Therapy

Maintenance therapy should start 4 weeks after completion of adjuvant therapy.

- Patients in the control arm (Arm A) will receive nivolumab alone on Day 1 of every 4 week cycle for up to 24 cycles (Cycles 13-36).
- Patients in the experimental arm (Arm B) will receive nivolumab on Day 1 of every 4 week cycle for up to 24 cycles (Cycles 13-36) and FVP-CV301 will be given concomitant every twelve weeks (every 3 cycles) for 8 doses.

Post-therapy patients will be under surveillance per NCCN guidelines with repeat CEA every 3 months for 2 years followed by every 6 months for 1 year (total 3 years), repeat CT of the C/A/P every 3 months for 2 years followed by every 6 months for up to 1 year (total 3 years), and colonoscopy at one year with repetition based on findings at the time of the procedure.

In the event of recurrence, the patient's disease and next line of therapy will be managed according to the individual cancer center's disease group management team. If the recurrence is within two years, the patient will continue to receive their scheduled nivolumab ± vaccine. In the event that administration of nivolumab ± vaccine is impacting the delivery or tolerability of standard of care next line therapy, patients will be removed from protocol therapy but will continue to be followed on study.

5.2 mFOLFOX6

5.2.1 Preparation and Administration

For detailed information on these agents, refer to the FDA approved package inserts. Institutional standards may be utilized for the preparation and administration of mFOLFOX6 including windows for infusion times. mFOLFOX6 will be administered as a combination regimen (see Table below) every 14 days for 4 cycles prior to surgery then every 14 days for 8 cycles after surgery after clearance to resume chemotherapy at the discretion of the performing surgeon. Subjects that do not proceed to surgery may begin chemotherapy

A histamine-2 (H2) antagonist, a histamine-1 (H1) antagonist, and a steroid may be used as premedications to decrease the risk of hypersensitivity reactions.

Consider the below premedication supportive care regimen; institutional standards may be used for premedication supportive care regimen.
Ondansetron 24 mg PO prior to Chemotherapy
Dexamethasone 12 mg PO
Ondansetron 8 mg PO every 12 hours for 2 days
Dexamethasone 8 mg PO every 12 hours for 2 days
Prochlorperazine 10mg IV/PO q6hr PRN Nausea/Vomiting

5.2.2 mFOLFOX6 Dosing

The recommended doses and routes of administration for the mFOLFOX6 should be made according to institutional guidelines, but a typical dose/schedule is detailed in the table below. Windows for administration may be utilized as per institutional standards including windows for infusion times.

*For oxaliplatin doses ≤ 104 mg use 250 mL D5W.

Drug	*Dose Per Unit*	*Route*	*Total Volume and Rate*
Oxaliplatin*	85 mg/m^2	IVPB	D5W 250-500 mL over 2 hours
Leucovorin	400 mg/ m^2	IVPB	NS 250 mL over 2 hours
Fluorouracil	400 mg/ m^2	IVP	Over 5 minutes after leucovorin
Fluorouracil	2400 mg/ m^2	IVCI	Diluted in NS over 46 hours

5.2.2.1 Oxaliplatin

- Oxaliplatin administration must always precede the administration of 5-FU.
- Oxaliplatin may be given at the same time as leucovorin in separate bags using a Y connector (providing trometamol is not used as an excipient).
- Oxaliplatin may not be administered with fluorouracil.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Oxaliplatin causes irritation if extravasated (follow local policy).
- Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to cold, therefore cryotherapy should be avoided.
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Unopened vials should be stored at 15-30°C; protect from light.

5.2.2.2 Leucovorin

- Leucovorin may be given at the same time as oxaliplatin in separate bags using a Y connector (providing trometamol is not used as an excipient).
- Leucovorin must be given prior to fluorouracil (enhances the effects of fluorouracil by increasing fluorouracil binding to target enzyme thymidylate synthetase).
- Infuse IV over 2 hours using CADD pump or similar device.

5.2.2.3 Fluorouracil

- Infuse through central venous access device if available. Infuse through peripheral venous catheter if infusion for only 3-5 days.
- Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation.
- Fluorouracil is incompatible with doxorubicin, epirubicin, diazepam, methotrexate, and cytarabine. Line must be flushed between administration of fluorouracil and these agents.
- Give IV bolus slow push through sidearm of free-flowing IV (D5W or NS) over 5 minutes.
- Infuse IV continuous infusion over 46 hours using CADD infusion pump or similar device.

5.3 CV301

5.3.1 MVA-BN-CV301

One MVA-BN-CV301 vaccine vial has a nominal titer of 4 x 10^8 infectious units (Inf.U) in 0.5 mL of the drug product. The composition of 1 dose of MVA-BN-CV301 is described below:

Component	Quantity per Dose (0.5 mL)	Function
Active substance		
Live attenuated vaccinia virus, strain MVA-BN-CV301	Nominal Titer 4 x 10^8 Inf.U	Active substance, immunizing antigen
Excipients		
Trometamol (Tris-hydroxymethyl-amino methane)	0.605 mg (10 mM)	Excipient Component of formulation buffer
Sodium Chloride	4.090 mg (140 mM)	Excipient Component of formulation buffer

5.3.2 FPV-CV301

One FPV-CV301 vaccine vial has a nominal virus titer of 1 x 10^9 Inf.U in 0.5 mL of the drug product. The composition of 1 dose of FPV-CV301 is described below:

Component	Quantity per Dose (0.5 mL)	Function
Active substance		
Live recombinant vaccinia virus, strain FPV-CV301	Nominal Titer 1 x 10^9 Inf.U	Active substance, immunizing antigen
Excipients		
Sodium Chloride	3.6 mg (123.2 mM)	Excipient Component of formulation buffer
Potassium Chloride	0.09 mg (2.4 mM)	Excipient Component of formulation buffer
Potassium Dihydrogen Phosphate	0.09 mg (1.3 mM)	Excipient Component of formulation buffer
Potassium Chloride	0.09 mg (2.4 mM)	Excipient Component of formulation buffer
Potassium Dihydrogen Phosphate	0.09 mg (1.3 mM)	Excipient Component of formulation buffer

Detailed trial-specific instructions on the preparation and administration of MVA-BN-CV301 and FPV-CV301 are provided in a separate Pharmacy Manual supplied to each clinical trial site.

5.3.3 CV301 Dosing

The following dosing is based on the experience in a phase I clinical trial. Trial CV301-2015-201 is an ongoing, BN-sponsored Phase 1/2 Trial of CV301 in Combination with Nivolumab versus Nivolumab in Subjects with Previously Treated Non-Small Cell Lung Cancer.

In the phase I part of this trial, 12 subjects with various CEA/MUC-1 positive cancers have been enrolled, 6 male and 6 female subjects, aged between 39 and 77 years. Of these 12 subjects, 3 have received MVA-BN-CV301 at the lowest dose level, 4 x 10^8 Inf.U., 3 have received the second dose level, 8 x 10^8 Inf.U., and 6 have received the highest dose level, 1.6 x 10^9 Inf.U.

At the cut-off date for assessment of the initial phase I safety data, 3 of the subjects had also received at least one dose of FPV-CV301, at a dose of 1 x 10^9 Inf.U./0.5 mL.

Initial safety data from the phase I part of this trial involving 12 subjects dosed in three different dose levels show that almost all reported AEs refer to expected (solicited) local and general reactions, including injection site reactions, fever/chills, headache, fatigue, myalgia/arthralgia, and flu-like symptoms. There was no occurrence of any of the pre-specified adverse events of special interest (immune-related events and cardiac events). There were no related SAEs. There were no dose-limiting toxicities at all three investigated dose levels of MVA-BN-CV301. Based on this initial safety information, the trial has moved into the phase Ib part, which includes combination treatment of CV301 and Nivolumab. The selected dose level for the further course of the trial was 1.6 x 10^9 Inf.U. (i.e. 4 injections of 4 x 10^8 Inf.U./0.5 mL) of MVA-BN-CV301.

5.3.4 MVA-BN-CV301

The dose for MVA-BN-CV301 is 4 injections of 4 x 10^8 infectious units/0.5 mL given subcutaneously prior to the start of nivolumab on Days -28 and -14. All injections will be given at the same clinic visit.

5.3.5 FPV-CV301

The dose for FPV-CV301 is 1 dose of 1 x 10^9 infectious units/0.5 mL given subcutaneously prior to the start of nivolumab at least one hour prior to mFOLFOX6 on Day 1 of Cycles 1-4, and FVP-CV301 boosters given every 2 weeks through completion of chemotherapy on Cycles 5-12, FVP-CV301 will then be administered every twelve weeks.

5.4 Nivolumab Dosing

Nivolumab is safe and well tolerated up to 10mg/kg Q2W. For this study, the standard every 2-week Nivolumab dose of 240 mg IV (identical to a dose of 3 mg/kg for subjects weighing 80 kg) was selected based on clinical data, modeling and simulation approaches using population PK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and renal cell carcinoma) where body weight normalized dosing (mg/kg) has been used. Pre-operatively, participants will receive nivolumab at a dose of 240 mg as a 30 minute infusion every 2 weeks (starting with chemotherapy in the control arm Cycles 1-4 and starting with the vaccine in the experimental arm Days -28, -14 then Cycles 1-4). Post-operatively nivolumab will be given at a dose of 240 mg IV every 2 weeks concurrently with chemotherapy ± vaccine for 8 chemotherapy cycles (Cycles 1-8). After Cycle 8 (completion of chemotherapy), nivolumab will be given concurrently with the vaccine. Nivolumab will be given every 4 weeks at the standard every 4-week dosing of 480 mg IV for up to 24 cycles and the vaccine will be given every 12 weeks. An infusion window of ± 10 minutes may be applied.

5.5 Supportive Care

Anti- emetics: Moderate emetogenicity. Follow local anti-emetic policy.

Anti-diarrheals: Follow local anti-diarrheal policy.

Premedications for hypersensitivity: Not usually required unless the patient has had a previous hypersensitivity. H1 or H2 blockers or steroids as pre-medication or for chills/fever /rigor during the infusion if required.

Treatment of dermatologic reactions may include topical moisturizers (containing urea, salicylic acid or ammonium lactate), sunscreen (SPF>15 UVA/UVB), topical steroids (e.g. clobetasol), and topical (e.g. lidocaine) and/or oral pain relievers (e.g. ibuprofen, naproxen, or celecoxib). Advise patients to limit the use of hot water, take cool showers or baths, pat skin dry/avoid rubbing of hands or feet, apply ice packs or cool wet towels, avoid the sun/sources of heat, avoid harsh chemicals, avoid walking barefoot and wear loose-fitting clothing.

Mouthwashes (e.g. Caphasol, grade III mouthwash) may be prescribed for mucositis to be used as needed.

5.6 Reproductive Information

There is no information about how an immune response against CEA and MUC-1 might affect sperm function, egg function, or growth of an unborn baby. It is not recommended to become pregnant, breast feed, father children or donate sperm from the time of informed consent until 4 months after the last dose of vaccine. For those subjects, that do not receive the vaccine this is not applicable and information below provides timeframe for birth control.

Nonclinical findings suggest for Nivolumab a potential risk to human pregnancy. Hence, Nivolumab dosing during pregnancy is prohibited. In addition, women of childbearing potential (WOCBP) receiving Nivolumab will be instructed to adhere to contraception from the time of informed consent, during treatment and for 5 months after the last dose of Nivolumab. This timeframe is also applicable to breastfeeding. Men receiving Nivolumab are not required to use contraception but consideration should be given for the timeframe outlined per package insert for chemotherapy. This also applies to donation of sperm.

The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

5.7 Concomitant Medications

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Subjects who are still being followed for a serious adverse events (SAE) will have SAE-specific concomitant medications recorded until resolution of the SAE. For specific information regarding the use of concomitant medications with study drug(s) please refer to the appropriate IB.

5.7.1 Allowed Concomitant Medications

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

5.7.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The site investigator should discuss any questions regarding this with the sponsor-investigator via the HCRN project manager. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.
The following medications are excluded while the subject is receiving study drugs:

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors
- Any additional anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy, will not be allowed, even if utilized as treatment of non-cancer indications.
- Any therapeutic investigational agents
- Radiation therapy**; NOTE:** Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with Sponsor Investigator. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids (>10 mg prednisone equivalent) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as premedication for contrast allergy or for COPD exacerbation). Inhaled or topical steroids, and adrenal replacement doses of steroids (for example prednisone 10mg daily) are permitted while on study.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICIATIONS

Guidelines for dose delays and dose modifications are described below, and applicable to the start of each cycle as well as during the cycle if treatment-related toxicities occur. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

Dose modifications are always based on the dose used in the previous cycle.

The investigator may attribute each toxicity event to the vaccine, nivolumab, mFOLFOX6, or any component of the combination therapy. Reduction or holding of one agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is related to one of the study drugs. For example, if mFOLFOX6 is held due to an AE attributed to that component or the combination, then the vaccine and/or Nivolumab may continue to be administered. The drug to which the investigator is attributing the AE must be documented. If` there is more than a 2-day delay for any reason, administration of study drugs should be re-aligned so that the chemotherapy falls within +2 days with the next cycle.

6.1 mFOLFOX6

Contraindicated in: Hypersensitivity to oxaliplatin, severe renal impairment (CrCl < 30 mL/min), pregnant/breastfeeding, peripheral neuropathy with severe functional impairment prior to the first cycle. Use caution in patients with: Previous pelvic radiotherapy, recent myocardial infarction, uncontrolled angina, uncontrolled hypertension, uncontrolled cardiac arrhythmias, uncontrolled congestive heart failure, baseline > 3 loose bowel movements per day (in patients without colostomy or ileostomy), symptomatic peripheral neuropathy. Toxicities include: myelosuppression ± infection, neuropathy, nausea, vomiting, diarrhea, transaminitis, fatigue, mucositis, abdominal pain, bleeding, rash, hand-foot syndrome, pharyngolaryngeal dysesthesia, arterial or venous thromboembolism, venous occlusive disease, hypersensitivity reaction, cardiotoxicity, hemolytic uremic syndrome, nephrotoxicity, pancreatitis, pneumonitis, rhabdomyolysis, RPLS.

The following dose reductions should be used for all toxicities:

Agent	**Dose Level 0**	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	Discontinue
Leucovorin	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
Fluorouracil	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2	Discontinue

*Leucovorin is delayed or omitted if bolus fluorouracil is delayed or omitted
*Institutional standards for measuring height and weight during chemotherapy administration should be used and dose adjusted according to institutional standards.

6.1.1 Renal Impairment

mFOLFOX6 is contraindicated in severe renal impairment (CrCl < 30 mL/min).

CrCl (mL/min)	*Oxaliplatin*	*Leucovorin*	*Fluorouracil*
50-80	No change	No change	No change
30-49	No change, monitor	No change	No change, monitor
<30	Discontinue	No change	Consider dose reduction to next lower dose level

6.1.2 Hepatic Impairment

Limited data are available regarding patients with hepatic impairment.

Bilirubin		*AST/ALT*	*Oxaliplatin*	*Leucovorin*	*Fluorouracil*
Bilirubin ≤ 2 x ULN			No change	No change	Caution
Bilirubin > 2-4 x ULN	and/or	AST/ALT 2-4 x ULN	No change	No change	Caution
Bilirubin > 4 x ULN	and/or	AST/ALT > 4 x ULN	No data available	Omit if 5FU omitted	OMIT if bilirubin > 4 x ULN

6.1.3 Hematologic Toxicity

Neutropenia

Fever or other evidence of infection must be assessed promptly and treated aggressively.

Grade	*ANC (x 10^9/L)*
1	≥ 1.2
2	1.0-1.19
3	0.5-0.99
4	< 0.5

*If ANC < 1.2 on day 1 of cycle, hold treatment and check weekly CBC
*If ANC ≥ 1.2 within 4 weeks, proceed at dose level across from nadir ANC
*If ANC remains < 1.2 after 4 weeks, discontinue treatment

Dose modification

	Dose Level Subsequent Cycles	
Grade	*Oxaliplatin*	*Fluorouracil*
1	Same dose level	Same dose level
2	Same dose level	Same dose level
3	Decrease 1 dose level	Same dose level
4	Decrease 1 dose level	Omit bolus Decrease CI 1 dose level
Neutropenic Fever	Omit until neutropenic fever resolves. Consider decreasing 2 dose levels.	
Sepsis/septic shock	Discontinue	Discontinue

Thrombocytopenia

Grade	*Platelets (x 10^9/L)*
1	≥ 75
2	50-74.9
3	10-49.9
4	< 10

*If platelets < 75 on day 1 of cycle, hold treatment and check weekly CBC
*If platelets ≥ 75 within 4 weeks, proceed at dose level across from nadir platelet count
*If platelets remain < 75 after 4 weeks, discontinue treatment

Dose modification

	Dose Level Subsequent Cycles	
Grade	*Oxaliplatin*	*Fluorouracil*
1	Same dose level	Same dose level
2	Same dose level	Same dose level
3	Decrease 1 dose level	Same dose level
4	Decrease 2 dose levels	Same dose level

6.1.4 Peripheral Sensory Neuropathy

Neuropathy may be partially or wholly reversible after discontinuation of therapy.

Grade	*Symptoms*
1	Asymptomatic Mild paresthesias Loss of deep tendon reflexes
2	Moderate symptoms Limiting instrumental ADLs
3	Severe symptoms Limiting self-care ADLs
4	Life-threatening consequences Urgent intervention indicated
5	Death

Dose modification

		Dose Level Subsequent Cycles	
Grade		*Oxaliplatin*	*Fluorouracil*
1		Same dose level	Same dose level
2 (persistent)		Decrease 1 dose level	Same dose level
3	1st occurrence	Decrease 1 dose level	Same dose level
	2nd occurrence	Decrease 1 dose level	Same dose level
	Persistent	Discontinue	Same dose level
4		Discontinue	Same dose level

*Patients with good recovery from Grade 3 neuropathy may be considered for re-challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

6.1.5 Gastrointestinal Toxicity

mFOLFOX6 can cause nausea, vomiting, and diarrhea. Prophylactic and/or therapeutic anti-emetic and anti-diarrheal therapies are warranted. Caution is advised in patients with baseline of > 3 loose bowel movements per day. Severe diarrhea/emesis can result from the combination of oxaliplatin and 5FU. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal failure may be caused by severe diarrhea/emesis. In patients with diarrhea, treatment should be delayed until symptoms reach a level of Grade 2 or less.

Grade	*Symptoms*
1	Increase < 4 stools per day over baseline Mild increase in ostomy output over baseline
2	Increase of 4-6 stools per day over baseline Moderate increase in ostomy output over baseline
3	Increase of ≥ 7 stools per day over baseline Severe increase in ostomy output over baseline Incontinence Hospitalization indicated Limiting self-care ADLs
4	Life-threatening consequences Urgent intervention indicated
5	Death

6.1.6 Mucositis

In patients with mucositis, treatment with 5-FU should be delayed until symptoms reach a level of Grade 2 or less.

Grade	*Symptoms*
1	Asymptomatic or mild symptoms; Intervention not indicated
2	Moderate pain; Not interfering with oral intake; Modified diet indicated
3	Severe pain; Interfering with oral intake
4	Life-threatening consequences; Urgent intervention indicated
5	Death

6.1.7 Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome)

This has been reported as an unusual complication of high dose bolus or protracted continuous therapy with fluorouracil causing redness, swelling, and pain on the palms of the hands and/or the soles of the feet, sometimes with blistering. Although less common, it may occur elsewhere on the skin such as the knees or elbows. Treatment is supportive including moisturizing creams, topical anti-inflammatory medications, and topical or oral pain relievers. Patients should limit the use of hot water, take cool showers or baths, pat skin dry/avoid rubbing of hands or feet, apply ice packs or cool wet towels, avoid the sun/sources of heat, avoid harsh chemicals, avoid walking barefoot and wear loose-fitting clothing.

6.1.8 Pharyngolaryngeal Dysesthesia

Acute pharyngolaryngeal dysesthesia occurs in 1-2% of patients. It is characterized by subjective sensations of dysphagia and dyspnea without objective evidence of respiratory distress, laryngospasm or bronchospasm (e.g. cyanosis, hypoxia, wheezing, stridor). Symptoms are often precipitated by exposure to cold. The symptoms are rapidly reversible in the absence of treatment, but antihistamines and bronchodilators may be administered. Increasing the infusion time from 2 to 6 hours helps reduce the incidence of this syndrome.

6.1.9 Venous Occlusive Disease

This is a rare but serious complication that has been reported in 0.02% of patients receiving oxaliplatin in combination with fluorouracil. VOD can lead to hepatomegaly, splenomegaly, portal hypertension and esophageal varices. Patients should be instructed to report any jaundice, ascites, or hematemesis immediately.

6.1.10 Hypersensitivity Reaction

Patients may experience platinum hypersensitivity. Special surveillance must be ensured for patients with a history of allergic manifestations to other products containing platinum. Therapies to treat anaphylaxis must be present when chemotherapy is administered. In the case of anaphylactic manifestations, the infusion should be interrupted immediately and appropriate symptomatic treatment started. Re-administration of oxaliplatin is contraindicated.

6.1.11 Cardiotoxicity

Cardiotoxicity, particularly angina and myocardial ischemia/infarction, is a serious complication of treatment with fluorouracil. Patients should be monitored carefully during therapy, particularly those with a prior history of cardiac disease or other risk factors. Patients with a history of cardiac disease should have a baseline ECG prior to starting therapy.

6.1.12 Hemolytic Uremic Syndrome (HUS)

HUS should be suspected and oxaliplatin therapy interrupted when hematocrit is $< 25\%$, platelets $< 100{,}000$, and creatinine ≥ 1.5 mg/dL. If HUS is confirmed, oxaliplatin should be permanently discontinued.

6.1.13 Pneumonitis

In the event of unexplained respiratory symptoms (e.g. non-productive cough, dyspnea, crackles or radiological pulmonary infiltrates), discontinue oxaliplatin until interstitial lung disease (ILD), pneumonitis or pulmonary fibrosis is excluded.

6.1.14 Additional Considerations

Dihydropyrimidine dehydrogenase (DPD) deficiency

Deficiency in the dihydropyrimidine dehydrogenase enzyme can cause rare, life-threatening toxicities (e.g. stomatitis/mucositis, neutropenia, neurotoxicity, and diarrhea) following the administration of fluorouracil. Severe, unexplained toxicities require further investigation prior to continuing treatment.

Drug Interactions

- Fluorouracil administration can cause marked elevations of prothrombin time (PT) and INR in patients stabilized on warfarin therapy. Monitor PT/INR at baseline and as clinically indicated while on therapy.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin. Caution in patients with seizure disorders on phenytoin therapy.
- Caution when administering fluorouracil in conjunction with medications that may affect dihydropyrimidine dehydrogenase levels/activity.

Please see individual FDA package inserts for full drug interaction information.

6.2 CV301

In all completed and ongoing clinical trials, vaccinations with MVA-BN have shown to be generally safe and well tolerated. No cases of death, assessed as being even possibly related, have been reported for a subject in a clinical trial using MVA-BN. Results obtained from completed Phase 1 and 2 trials and ongoing trials with several recombinant MVA-BN based vaccines in healthy adults and children, HIV infected and cancer subjects demonstrate a similar safety profile as MVA-BN alone. Additional information on the safety profile of MVA-BN and recombinant MVA-based vaccines is provided in the Investigator's Brochure.

There are no dose modifications for CV301. In the case of an allergic reaction or an auto-immune response causing a serious adverse event thought to be related by the investigator to CV301, treatment would be stopped.

6.3 Nivolumab

There will be no dose escalations or reductions of nivolumab allowed. Premedications are not recommended for the first dose of nivolumab. Participants should be carefully monitored for infusion reactions during nivolumab administration. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Guidelines on the recommended management are provided in the Investigator Brochure.

Nivolumab administration should be <u>delayed</u> for the following:

- Given hepatic involvement as an inclusion criteria, continue, withhold or permanently discontinue nivolumab based on the severity of hepatitis and baseline AST and ALT levels (following guidelines for use of nivolumab in HCC liver disease):
  - If AST/ALT is within normal limits at baseline and increases to > 3-5x the ULN, withhold dose
  - If AST/ALT is > 1-3x ULN at baseline and increases to > 5-8x the ULN, withhold dose
  - If AST/ALT is > 3-5x ULN at baseline and increases to > 8x the ULN, withhold dose
- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met. In general, in the event of a grade 2 AE, treatment with nivolumab can be resumed when the AE has resolved to ≤ grade 1.

Nivolumab treatment should be permanently discontinued for the following:

- If AST/ALT increases to > 10x the ULN or total bilirubin increases to > 3x ULN, permanently discontinue (following guidelines for use of nivolumab in HCC liver disease).
- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

6.3.1 Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with Nivolumab. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (e.g., focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. At this time, no other underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has yet to be identified. Asymptomatic subjects were typically managed with dose delay. Subjects with Grade 2 pneumonitis were managed with dose delay, treated with corticosteroids, and had resolution of pneumonitis within days to weeks. In cases where Nivolumab treatment was restarted, recurrence of pneumonitis was infrequently reported across the Nivolumab program. Subjects with more severe cases of pneumonitis can be difficult to treat. In a few cases, subjects who did not initially respond to corticosteroids were administered anti-tumor necrosis factor therapy (infliximab) and/or cyclophosphamide. In some of these cases, pneumonitis began to resolve following the use of these additional therapies.

Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. For symptomatic Nivolumab-related pneumonitis, the principal treatment is corticosteroids. All subjects with Grade 3-4 pneumonitis should discontinue Nivolumab and initiate treatment with high doses of corticosteroids. Consultation with a sponsor-investigator should be sought for all suspected cases of pneumonitis.

6.3.2 Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with Nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved. Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. As GI symptoms are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., infection or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade GI AEs is corticosteroids. Caution should be taken in the use of narcotics in subjects with diarrhea, colitis, or abdominal pain as pain medicines may mask the signs of colonic perforation. Consultation with a sponsor-investigator should be sought for all moderate- and high-grade cases of GI AEs.

6.3.3 Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug induced liver injury (DILI), have been observed following treatment with Nivolumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved. Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each Nivolumab treatment. As LFT abnormalities are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids. Consultation with a sponsor-investigator should be sought for all moderate- and high-grade hepatic AEs.

6.3.4 Endocrinopathies

Endocrinopathies have been observed following treatment with Nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were

managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, Nivolumab treatment was held until adequate hormone replacement was provided. Early recognition and treatment of endocrinopathies are critical to its management. Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, anemia, concomitant medications, or depression) and a possible drug-related AE as the management can be quite different. The principal management of endocrinopathies is hormone replacement therapy. For subjects with moderate- or high-grade events, corticosteroids may also be used. Consultation with a sponsor-investigator should be sought for all moderate- and high-grade cases of endocrinopathies.

6.3.5 Skin Adverse Events

Rash and pruritus were the most common skin AEs observed following treatment with Nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids. Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. Other drugs that may cause rash should be considered in the differential and, if possible, discontinued. In addition, careful evaluation of potential benefit-risk is necessary when considering the use of Nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior immune-stimulating therapy. The principal treatment for skin AEs, such as rash and pruritus, consists of symptomatic management. Topical corticosteroids can be used for low- to moderate-grade focal rash. Systemic corticosteroids should be used for diffuse and high-grade rash. Consultation with a Sponsor's medical monitor should be sought for all moderate- and high-grade cases of skin AEs. Rare cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been observed. If symptoms or signs of SJS or TEN appear, Nivolumab should be withheld and the patient referred for specialized care for assessment and treatment. If the patient has confirmed SJS or TEN, permanent discontinuation of Nivolumab is recommended.

6.3.6 Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with Nivolumab. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved. Physicians should monitor creatinine regularly. As creatinine abnormalities are common in subjects with cancer and other comorbidities, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., dehydration, concomitant medications, hypotension, or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for renal AEs

is corticosteroids. Consultation with a sponsor-investigator should be sought for all moderate- and high-grade cases of renal AEs.

6.3.7 Neurologic Adverse Events

Neurologic AEs have been uncommonly observed following treatment with Nivolumab. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality). Early recognition and treatment of neurologic AEs is critical to its management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (e.g., weakness), changes in sensation (e.g., numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, concomitant medications, or infection) and a possible drug-related AE as the management can be quite different. The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin. For high-grade related neurological AEs, Nivolumab should be discontinued. Consultation with a sponsor-investigator should be sought for all moderateand high-grade cases of neurologic AEs.

6.3.8 Infusion Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of Nivolumab are uncommon. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty in breathing during and immediately after administration of Nivolumab.

6.3.9 Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported. As lipase/amylase abnormalities are not uncommon in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, concomitant medications, or alcohol) and a possible drug-related cause as the management can be quite different. The recommended management of Nivolumab-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately on a weekly basis, and Nivolumab should be held per protocol instructions. For sustained asymptomatic Grade 4 elevations, Nivolumab should be discontinued per protocol instructions. For subjects with elevated lipase/amylase and symptoms consistent with possible pancreatitis, Nivolumab should be discontinued, and consultation with a gastroenterologist should be considered. Consultation with a sponsor-investigator should be sought for all high-grade cases of elevated lipase/amylase.

6.3.10 Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Consultation with the sponsor-investigator should be sought for all cases of ocular inflammatory events. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause. Vogt-Koyanagi-Harada syndrome (VKH) is a T-cell mediated autoimmune attack on melanocytes. VKH manifests as a multi-system disorder characterized by granulomatous panuveitis with exudative retinal detachments, often associated with neurologic and cutaneous manifestations. Rare cases have been observed. Based on the severity of the adverse reaction, Nivolumab should be withheld or discontinued, and corticosteroids administered accordingly.

6.3.11 Other Immune-mediated Adverse Events

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, Nivolumab should be withheld or discontinued, and corticosteroids administered accordingly. Upon improvement, Nivolumab may be resumed after corticosteroid taper. If there is recurrence of any Grade 3 or 4 immune-related adverse reactions or life-threatening immune-related adverse reactions, Nivolumab must be permanently discontinued. Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with Nivolumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, Nivolumab should be withheld or discontinued, and appropriate treatment instituted. For grade 3 myocarditis, Nivolumab should be permanently discontinued.

6.3.12 Criteria to Resume Nivolumab Dosing

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

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the site sponsor-investigator

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the sponsor-investigator. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Intercurrent illness or SAE that prevents further administration of treatment
- Noncompliance with treatment plan
- Site investigator determines a change of therapy would be in the best interest of the subject
- Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the sponsor-investigator
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant

6.5 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

1 cycle = 14 days during neoadjuvant and adjuvant treatment 1 cycle = 28 days during maintenance treatment A = Arm A and B = Arm B	Screen	**Arm B** ± 2 days		Neoadjuvant Therapy C1- C4	Pre-Surgery	Surgery or Biopsy	Adjuvant Therapy C5-C12[7]	Maintenance C13-36[11]	Safety Visits D30/D100[12]	Follow up[13]
	D-28	D-28	D-14	± 2 days			± 2 days	D1 ± 2 days	+7 days	± 14 days
REQUIRED ASSESSMENTS										
Informed Consent	X									
Medical History including smoking history[1]	X									
Physical Exam[2]	X	B	B	X	X		X[2]	X	D30	X
Vital signs ECOG Performance Status[2]	X	B	B	X	X		X	X	D30	X
ECG	X				X		C5D1			
AEs & concomitant medications	X	B	B	X	X		X	X	X	X
LABORATORY ASSESSMENTS										
Complete Blood Cell Count with diff (CBC)	X	B	B	X	X		X	X	D30	
Comprehensive Metabolic Profile (CMP)	X	B	B	X	X		X	X	D30	
CEA and CA19-9[3]	X				X		C8D1	X[11]		X[12]
PT/INR and aPTT[4]	X				X					
Thyroid Function[4]	X	B		X	X		X[4]	X[4]		
Amylase & Lipase[4]	X	B	B	X			X[4]	X[4]		
Pregnancy test (serum or urine) (WOCBP)[5]	X[5]	B	B	X[5]			X[5]	X[5]		
DISEASE ASSESSMENT										
CXR[10]					X					
CT or PET of chest[6]	X				X[6]		X[6]	X[6]		X[6]
CT or MRI of abdomen and pelvis [6]	X				X[6]		X[6]	X[6]		X[6]
TREATMENT EXPOSURE[7]										
mFOLFOX6				X			X			
Nivolumab		B	B	X			X	X		
Vaccination (Arm B ONLY)		B	B	X			X	X		
SPECIMEN COLLECTION										
Tumor Biopsy[8]	X					X[8]				
Blood sample for genomic DNA[9]		B		A						
Blood Samples for correlative research[9]		B		A	X		X[9]			
FOLLOW-UP										
Survival Status, Subsequent Therapy										X

CBC with differential to include Hgb, Hct, RBC, WBC, ANC, platelet, MCV and CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin (direct bilirubin if total is elevated), alkaline phosphatase

Key to Footnotes

1: Medical History. In addition, the following data will be obtained: smoking history questionnaire and a question about how the subject heard about the study. Prior treatment for colon cancer or other malignancies should be noted. If previously treated for colon cancer information regarding diagnosis, staging, treatment, and response should be obtained. Results of prior genomic testing will be requested and are required if available.

2: Physical exams during pre-surgery treatment should be performed on Cycle 1 and Cycle 3. The pre-surgery visit should include evaluation by both the medical and surgical oncologist. Physical exams during post-surgery treatment should be performed on Cycle 5, Cycle 7, Cycle 9, and Cycle 12. During maintenance treatment, physical exams should occur every 28 days (Day 1 of each cycle). Additional physical exams may be performed at the site investigator's discretion. Vital signs to include blood pressure, weight, and height (screening only). Treatment BSA and ECOG performance status should be documented as well.

3: CEA and CA19-9 at screening, prior to surgery, post-surgery Cycle 8 and per Footnote 11.

4: Coagulation studies at screening and prior to surgery, then per investigator's discretion during treatment. Amylase and lipase will be performed at screening and prior to each treatment with nivolumab +/- vaccine. TSH, T3 and T4 to be performed; free versus total T3/T4 is per investigator's discretion at screening, Day -28 (Arm B), Cycle 1, Cycle 3, at the pre-surgery evaluation then monthly. Thyroid testing may be done more frequently at investigator's discretion.

5: For women of childbearing potential (WOCBP): urine or serum βhCG, during screening then within 24 hours of initiation of study drug; only if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. WOCBP should be counseled on the importance of initiating birth control procedures from the time of screening and throughout treatment. Please see Section 5.6 for post treatment use of birth control. During treatment, a pregnancy test is required at least 2 days prior to each CV301 dose and every month of Nivolumab treatment. This may be a urine test done at home prior to dosing. Verbal results should be documented.

6: Patients that are registered must have confirmed isolated liver metastases by radiographic imaging. Baseline imaging must include the chest, abdomen, and pelvis by CT, PET/CT or triphasic CT. Re-staging imaging after neoadjuvant therapy to include CT, PET/CT or triphasic CT of the chest, abdomen/pelvis. Additional imaging required for surgical evaluation is at the surgical oncologist's discretion and can include an MRI in addition to restaging scans. Response will be assessed (1) prior to surgery/after 4 cycles of neoadjuvant therapy and (2) at completion of adjuvant therapy. Upon completion of adjuvant therapy, repeat imaging should occur every 3 months during maintenance. After completion of maintenance, imaging should occur every 3 months for 2 years followed by every 6 months for up to an additional year (total 3 years). The modality used for disease evaluation should be consistent throughout the study period.

7: Detailed description of study treatment can be found in Section 5. Arm A is the control arm and Arm B is the experimental arm. Post-surgery therapy will begin when the surgical oncologist deems the patient is ready and is clear of all infectious issues. For those subjects that do not undergo resection, post-surgery therapy may begin at treating physician discretion. The treatment order for Arm A is Nivolumab followed by mFOLFOX6. For Arm B the order of administration is vaccination prior to the start of nivolumab at least one hour prior to mFOLFOX6. A window of +2 days between administration of Nivolumab ± vaccination and mFOLFOX6 will be allowed. This window will accommodate subjects that receive their chemotherapy locally. If there is more than a 2-day delay for any reason, administration of study drugs should be re-aligned so that the chemotherapy falls within +2 days with the next cycle.

8: Required biopsies: Timepoints: (1) pre treatment tumor biopsy and (2) tumor biopsy at surgery or for unresectable subjects a fresh biopsy. The goal of collection is 50 mg of tumor tissue to be used for correlative testing. The site investigator and interventional radiologist should discuss the amount of cores that may be necessary to meet the goal of tissue collection. Testing on tumor tissue obtained pre- and post-therapy to include: PD-1 and PD-L1, mRNA signature by whole transcriptome sequencing using RNAseq TCR clonality assays and Immunoscore via IHC. The pre-treatment biopsy is required regardless of prior biopsy confirmation of metastatic CRC. If the subject does not undergo standard of care surgery after pre-surgery treatment, a research specific biopsy will be performed to obtain tissue for research purposes. There will be a cap of 10 fresh biopsies for unresectable subjects. Genomic testing results are required. FoundationOne platform is preferred, however results from an equivalent genomic platform may be used after discussion with the sponsor investigator. Please see the Correlative Laboratory Manual (CLM) for additional details.

9: Required blood collections: Blood will be collected prior to treatment for genomic DNA testing (Day -28 Arm B and Cycle 1 Day 1 Arm A). Testing on peripheral blood pre-therapy and post-therapy to include: Flow Cytometry, including CEA and MUC-1 antigen-specific immune response, and cytokines and serum soluble factors. Timepoints: (1) before vaccination (Arm B)/treatment (Arm A), (2) before surgery, (3) one month after surgery and (4) six months after surgery. In addition, blood for TCR clonality assays will be collected before vaccination (ARM B)/Treatment (ARM A), and 1 month post-surgery. Please see the Correlative Laboratory Manual (CLM) for additional details.

10. Additional pre-operative testing (such as routine pre-admission testing done prior to elective surgery) may be obtained as per institutional guidelines.

11. Detailed description of study treatment can be found in Section 5. Beginning 4 weeks after completion of adjuvant therapy, patients will continue on maintenance nivolumab but on the standard every 4-week schedule +/- vaccination every 12 weeks. A PE, AE assessment, laboratory assessment, and repeat CEA and CA19-9 will be done prior to each treatment. Additionally, participants will undergo re-staging CT C/A/P every 3 months as per current clinical practice standards. Upon completion of treatment, repeat CT of the C/A/P every 3 months for 2 years followed by every 6 months for up to 1 year (total 3 years).

12: Safety Follow Up: The D30 safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be monitored by a member of the study team until the event is resolved, stabilized, determined to be irreversible by the site investigator or a new anti-cancer treatment starts, whichever occurs earlier. The D100 safety follow up visit may be done via phone, email or other avenues as appropriate to assess for SAEs.

13: Upon completion of study treatment, patients should be under surveillance per NCCN guidelines with physical exam (PE), AE assessment, laboratory assessment, and repeat CEA every 3 months for 2 years followed by every 6 months for 1 year (total of 3 years). CT C/A/P will be done every 3 months for 2 years, followed by every 6 months for 1 year (total of 3 years). Colonoscopy at one year with repetition based on findings at the time of the procedure. The above are NCCN guidelines but if not followed, do not constitute a deviation from the protocol. Treating staff should monitor according to standard of care for patients receiving immunotherapy medications. If a patient progresses information regarding disease recurrence, anti-cancer treatment and response will be obtained. This may be done via phone call, email or other avenues as appropriate.

8. OVERVIEW OF MOLECULAR INVESTIGATIONS

- mRNA signature in tumor tissue pre- and post-therapy by whole transcriptome sequencing using RNAseq (by a lab such as Rutgers CINJ)
- Genomic profiling of metastatic and primary tumor DNA (by a lab such as FoundationOne®)
- CEA and MUC-1 antigen-specific immune response in pre- and post-therapy in peripheral blood by intracellular cytokine staining and/or ELISPOT or other validated assays.
- Other tumor-associated antigen-specific immune response measures may be assessed if adequate samples are available (by a lab such as Schlom lab, NIH)
- TCR clonality assays (by a lab such as Adaptive Biotechnologies®)
- Serum cytokine, and serum soluble factors (by a lab such as Schlom lab, NIH)
- PD-1/PD-L1 staining in pre- and post-therapy tumor tissue (by a lab such as Rutgers CINJ or Neogenomics)
- Immunoscore by IHC to be performed at a lab such as Rutgers CINJ

8.1 Tissue

8.1.1 Tissue prior to Treatment

A pre treatment tumor biopsy is required. The goal of collection is 50 mg of tumor tissue to be used for correlative testing. The site investigator and interventional radiologist should discuss the amount of cores that may be necessary to meet the goal of tissue collection. The pre-treatment biopsy is required regardless of prior biopsy confirmation of metastatic CRC.

Genomic testing results are required. FoundationOne platform is preferred, however results from an equivalent genomic platform may be used after discussion with the sponsor investigator. If genomic testing has not been performed, tissue should be submitted for testing per standard of care.

8.1.2 Surgical Tissue or Tissue from Biopsy

After neoadjuvant therapy, additional tissue will be obtained either at the time of surgery, or with a repeat biopsy if the patient is not a candidate for surgery, prior to further systemic or radiation treatment for the above mentioned correlates. There will be a cap of 10 fresh biopsies for unresectable subjects. The ideal amount of tumor tissue is 50 mg to be utilized for correlative analysis. The amount of cores to obtain this tissue is dependent on the type of core biopsy needle used. The site investigator should discuss this requirement with the appropriate physician performing the procedure.

Collection procedures will take place at individual participating institutions. Handling procedures will be performed according to participating site standard operating procedures (SOPs). Detailed shipping information regarding which specimens and the location for shipping are provided in the correlative laboratory manual (CLM). Shipping will be done in batches at intervals to be determined.

8.2 Peripheral Blood

Patients will have peripheral blood draws for isolation of peripheral blood mononuclear cells (PBMCs). Peripheral blood will be drawn (1) before vaccination on Day -28 (Arm B) or before Cycle 1 Day 1 (Arm A), (2) before surgery (both Arms), (3) one month after surgery for the above-mentioned correlates (both Arms) and (4) six months after surgery (both Arms).

Peripheral blood for PBMCs will be collected and then shipped unprocessed overnight by all participating sites. PBMCs will be isolated. Serum will be collected and shipped for cytokine analysis.

Whole blood will be sent for isolation of genomic DNA for TCR clonality assays before vaccination (ARM B)/Treatment (ARM A), and 1 month post-surgery.

Whole blood will be collected for genomic DNA prior to treatment for both Arms (Day -28 Arm B and Cycle 1 Day 1 Arm A).

8.3 Storage of Biospecimens

Any remaining samples after initial testing is done will be stored for future unspecified cancer related research. Permission to use these samples will be obtained from subjects during consent.

8.4 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

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

9.1.1 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.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as 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 subject, these are preferred for selection as target lesions.

9.3 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.

9.4 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.

9.5 Evaluation of Target Lesions

NOTE: See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 for special notes on the assessment of target lesions[21].

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
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
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).

9.6 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 subject 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 site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor-investigator.
Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.7 Definitions for Response Evaluation

9.7.1 Overall Survival
For the primary objective OS is defined as the date of metastasectomy to date of death from any cause.

9.7.2 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1 and surgical pathology defined as the percent tumor viability (see 9.7.3 for definition), from the start of treatment until disease recurrence.

9.7.3 Pathologic Complete Response Rate
This is defined as the extent of residual carcinoma assessed semiquantitatively by estimating the proportion of residual cancer cells as a percentage in relation to the total tumor area. The tumor area includes areas of chemotherapy-related tissue injury, tumor necrosis, and fibro-collagenous proliferation. Patients with a complete pathologic response would have no residual cancer cells

would be given 0%, while patients with no response would be given 100%. In patients with multiple tumor nodules, the mean of the values for the various tumor nodules should be reported.

9.7.4 Recurrence Free Survival

A measurement from the date of recurrence after metastasectomy by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.7.5 Perioperative Surgical Outcomes

Complications and their severities using the Clavien-Dindo classification for severity scores should be recorded.

10 DRUG INFORMATION

CV301 is the investigational agent involved in this study. mFOLFOX6 is an FDA approved regimen. Nivolumab is a human programmed death receptor-1 (PD-1) blocking antibody approved by the FDA at the dose of 240 mg every 2 weeks, and 480 mg every 4 weeks.

10.1 CV301

Please refer to the current version of the Investigator's Brochure (IB) for additional information regarding this vaccine.

CV301 is comprised of two recombinant poxviral vectors to be used together in a prime-boost vaccination regimen. The priming vector is a highly attenuated, non-replicating vaccinia virus Modified Vaccinia Ankara-Bavarian Nordic-CV301 (MVA-BN-CV301) and the boost is a recombinant fowlpox virus (FPV-CV301). Collectively, the regimen is referred to as CV301. CV301 has been designed to consist of five human transgenes to elicit a specific and robust immune response to a variety of cancers. Both viral vectors for CV301 co-express two human tumor-associated antigens (TAA): carcinoembryonic antigen (CEA) and mucin-1 (MUC-1), and three human costimulatory molecules: B7.1, intercellular adhesion molecule-1 (ICAM-1), and leukocyte function-associated antigen-3 (LFA-3) (or TRIad of COstimulatory Molecules, TRICOM™). The three costimulatory molecules are included to maximize the immune response to the TAAs. The anti-tumor mechanism of action for CV301 poxvirus-based immunotherapy is to induce the generation of tumor antigen-specific killer T cells capable of infiltrating the tumor. This tumor-specific T cell immune response is aimed to target and kill antigen-expressing tumor cells throughout the patient's body.

CV301 is a next-generation product based on the prior PANVAC recombinant vector-based therapeutic cancer vaccine, designed to induce an enhanced immune response against the CEA and MUC-1 antigens expressed by many carcinomas. Similarly, to CV301, the previous PANVAC regimen was comprised of two components: a vaccinia vector (PANVAC-V, inalimarev) and a fowlpox vector (PANVAC-F, falimarev), which were investigated for the treatment of a variety of carcinomas including breast, ovarian, colorectal, pancreatic and bladder carcinomas.

10.1.1 Supplier/How Supplied

Bavarian Nordic will supply CV301 at no charge to subjects participating in this clinical trial. MVA-BN-CV301 and FPV-CV301 are each supplied in 2 mL type I borosilicate glass vials closed with sterile bromobutyl rubber stoppers, crimped with aluminum caps and covered with polypropylene closures.

Supplies of both the MVA-BN-CV301 and the FPV-CV301 vaccines will be shipped temperature controlled and monitored to the clinical trial site. Both the MVA-BN-CV301 and the FPV-CV301 vaccines are stored -80°C at the drug depot, and shipped to and stored at the site at -80°C.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Storage, Preparation and Administration

MVA-BN-CV301 is a liquid-frozen, highly attenuated, live recombinant virus based on the viral vector MVA-BN. Packaging and vials will be labeled according to the respective product specifications.

FPV-CV301 is a liquid-frozen, highly attenuated, live recombinant virus. It is administered as subcutaneous application. The packages and vials will be labeled according to the respective product specifications.

Both the MVA-BN-CV301 and the FPV-CV301 vaccines must be stored at a temperature of -80°C ± 10°C or -20°C ± 5°C; in all cases avoiding direct exposure to light. A vial must not be re-frozen once it has been thawed. Once vaccines are stored at -20°C ± 5°C; storage at -20°C ± 5°C limits the vaccines' use to only 12 months starting with the date of the delivery. Please note that any vaccine stored at -20°C ± 5°C should not be switched to -80°C ± 10°C. It should remain in its current temperature and discarded after 12 months from the date of the delivery.

MVA-BN-CV301 and FPV-CV301 are administered via subcutaneous injection.

Used and unused vials need to be retained in a place with limited access until appropriate drug accountability has been performed. Drug accountability must be documented whenever the vaccine is either prepared or administered. After drug accountability has been performed, used and unused vials should either be returned to BN, to the designated drug depot, or discarded according to local regulations. Destruction or return of vaccine must be agreed upon with BN and appropriately documented. CV301 (MVA-BN-CV301 and FPV-CV301) is categorized as a biological safety level (BSL) 1 genetically modified organism. Therefore, CV301 and any materials that have been in contact with the product should be disposed of according to the respective institutional standards, local and occupational safety guidelines.

Detailed trial-specific instructions on the preparation and administration of MVA-BN-CV301 and FPV-CV301 are provided in a separate Pharmacy Manual supplied to each clinical trial site.

10.2 mFOLFOX

mFOLFOX6 is one of several chemotherapy regimens that include leucovorin calcium (calcium folinate), 5-fluorouracil and oxaliplatin, and which may be used in the treatment of advanced-stage and metastatic colorectal cancer.

For more information on these agents, refer to the FDA approved package inserts. These medications are commercially available.

10.2.1 Oxaliplatin

Oxaliplatin is a platinum alkylating agent, which contains platinum complexed to oxalate and diaminocyclohexane (DACH) complex. Platinum complexes are formed intracellularly and inhibit DNA synthesis through covalent binding of DNA molecules to form intrastrand and interstrand DNA cross-links. Oxaliplatin differs molecularly, from other platinums (cisplatin and carboplatin), by its bulky DACH carrier ligand that most likely accounts for both its efficacy and lack of cross-resistance with other platinum compounds. Cytotoxicity is cell-cycle nonspecific. Oxaliplatin is a radiationsensitizing agent.

*Oxaliplatin is incompatible with 0.9% NaCl.
*Oxaliplatin is incompatible in solution with alkaline medications or media and must not be mixed with these.

*Storage and handling materials containing aluminum parts that may come in contact with oxaliplatin should not be used for preparation or mixing of the drug, as aluminum can degrade platinum compounds.

1) The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution.

2) After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2º to 8°C (36º to 46° F)]. Do not freeze the concentrated solution.

3) The solution must be further diluted in an infusion solution of 250-500 mL of D5W. A final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions. Concentration must be between 0.2 to 0.7 mg/mL.

4) After final dilution with D5W, the shelf life is 6 hours at room temperature [20º to 25°C (68º to 77°F)] or up to 24 hours under refrigeration [2º to 8°C (36º to 46°F)].

5) Store under normal lighting conditions at 20°-25°C (68°-77°F); excursions permitted to 15-30°C (59- 86°F)]. Do not freeze.

10.2.2 Leucovorin

Leucovorin calcium (folinic acid) is a reduced form of folic acid. It is usually used 24 hours after methotrexate to selectively “rescue” normal cells from the adverse effects of methotrexate caused by inhibition of production of reduced folates. It is not used simultaneously with

methotrexate, as it might then nullify the therapeutic effect of the methotrexate. Leucovorin has also been used to enhance the activity of fluorouracil by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of thymidylate. Leucovorin is available in D and L stereoisomers; the L stereoisomer is the active moiety.

* Each 50, 100, and 200 mg vial of Leucovorin when reconstituted with 5, 10, and 20 mL, respectively, of sterile diluent yields a leucovorin concentration of 10 mg per mL. Each 350 mg vial of Leucovorin when reconstituted with 17.5 mL of sterile diluent yields a leucovorin concentration of 20 mg per mL. *Leucovorin should not be mixed in the same infusion as fluorouracil as a precipitate may form.

1) Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, use immediately and discard any unused portion. Because of the benzyl alcohol contained in Bacteriostatic Water for Injection, when doses greater than 10 mg/m2 are administered, Leucovorin should be reconstituted with Sterile Water for Injection, and used immediately.

2) Dilute leucovorin in 50-1000 mL D5W or NS for infusion. Lecovorin may be mixed in 50mL NS or D5W minibag (doses up to 500mg) or 100mL minibag (doses >500mg) or in 100mL fluid in graduated administration set (D5W, NS or 2/3-1/3). Parenteral admixture is stable for 24 hours stored at room temperature (25°C) and for 4 days when stored under refrigeration (4°C).

3) Lyophilized powder vials should be stored at 20° to 25°C (68° to 77° F). Solution for injection should be stored in refrigerator 2° to 8°C (36° to 46°F). Protect from light. Retain in carton until time of use.

10.2.3 Fluorouracil

Fluorouracil was developed based on the observation that tumor cells utilized the base pair uracil for DNA synthesis more efficiently than did normal cells of the intestinal mucosa. It is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP). The active form inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) occur especially with bolus administration. Fluorouracil is cell cycle phase-specific (S-phase).

*1 vial of Fluorouracil Injection contains: 500 mg fluorouracil in 10 ml solution (50 mg/ml); 1000 mg fluorouracil in 20 ml solution (50 mg/ml); 2500 mg fluorouracil in 50 ml solution (50 mg/ml); 5000 mg fluorouracil in 100 ml solution (50 mg/ml)

1) Fluorouracil may be mixed in a 50 mL minibag of NS or D5W, yielding a clear, colorless to light yellow solution. Solutions of fluorouracil are expected to be stable in solution 7 days at 37 °C, several weeks at 25 °C, and at least 4 months at 0-4 °C.

2) Store 5-fluorouracil in airtight containers protected from light.

10.3 Nivolumab

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered and sealed with aluminum seals. Vials must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

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 the protocol-specified doses for 30 minutes. It is not to be administered as an IV push or bolus injection.

At the fixed dose of 240 mg or 480 mg, Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. The administration of Nivolumab infusion must be completed within 24 hours of preparation.

Please refer to the current IB for preparation, storage and handling details regarding Nivolumab. Nivolumab will be supplied at no charge to patients on this study by BMS.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the sponsor-investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient whether or not considered related to the study vaccine. Either the condition was not present prior to signature of informed consent, or it has worsened in intensity or frequency following exposure to the study therapy. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol

- An intercurrent illness or injury that impairs the well-being of the subject

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

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

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

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs. Potential drug induced liver injury is defined as:

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

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the

pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.1.5 Cardiac events management

Based on the total clinical experience with poxvirus vectors for anticancer vaccines, including CV301's predecessor product PANVAC, a causal relationship of cardio-toxicity following treatment with CV301 and/or PANVAC is unlikely. Nonetheless, a proactive approach in pharmacovigilance will be applied prospectively, requesting from the investigators a deeper characterization of every case with a cardiac AE with the working hypothesis that myocarditis/pericarditis may be the underlying cause. As deemed necessary by the investigator, ECG and/or troponin testing may be performed in the presence of any cardiac symptoms, in order to exclude the diagnosis of myo-/pericarditis. The reporting of cardiac events follows the standard processes as outlined above.

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.

- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within The EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to Bavarian Nordic and Bristol Myers Squibb (BMS)

HCRN will report all SAEs to Bavarian Nordic (BN) at drug.safety@bavarian-nordic.com and BMS at Worldwide.Safety@BMS.com **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Bavarian Nordic and BMS **within 1 business day** as it is received from site.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to Bavarian Nordic's parent IND and BMS's parent IND at the time of submission. Additionally, HCRN will submit a copy of these documents to BN and BMS at the time of submission to FDA.

HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, HCRN will submit a copy of these reports to BN and BMS at the time of submission to FDA.

11.5 IND Safety Reports Unrelated to this Trial

BN and BMS will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system. Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

This is a multi-center, 1:1 randomized clinical trial comparing CV-301 vaccine to standard treatment in patients with resectable hepatic metastatic colorectal cancer.

12.2 Objectives and Endpoints

12.2.1 Definition of Primary Objective and Endpoint

Primary objective: We hypothesize that the addition of vaccination with CV301 to Nivolumab and perioperative systemic chemotherapy followed by complete surgical resection in patients with hepatic-limited metastatic colorectal cancer will significantly increase OS as compared to Nivolumab and perioperative systemic chemotherapy followed by surgical resection.

Primary Endpoint: 3-year OS between perioperative mFOLFOX6 plus Nivolumab and CV301 in combination with surgical resection in patients with hepatic-limited metastatic colorectal cancer. For the primary objective OS is defined as the date of metastasectomy to date of death from any cause.

12.2.2 Definition of Secondary Objectives and Endpoints

Recurrence-free survival, best overall response rate by RECIST 1.1 and surgical pathology criteria, proportion of patients amenable to complete resection/ablation upon first recurrence, incidence and severity of perioperative surgical complications as described above. In addition, a comparison of 3-year OS between the two groups as well as a comparison of OS in both groups to historical controls.

Secondary Endpoints: include 3-year recurrence-free survival, best overall response rate by RECIST 1.1 criteria and tumor pathology, perioperative complications and the proportion of patients able to undergo resection/ablation of first recurrences.

12.2.3 Correlative Objectives and Endpoints

Molecular correlates will also be obtained and descriptive statistics applied.

12.3 Sample Size and Accrual

This is a 1:1 randomized clinical trial comparing CV-301 vaccine to standard treatment in patients with resectable hepatic metastatic colorectal cancer. Based on a study by Morse et al. [17], the OS probability at 3 years is 0.588. We would like to detect an increase in OS in the CV-301 study arm with 80% power, using a 2.5% level one-sided log-rank test. This survival analysis will be from the time of metastasectomy.

With a sample size of 70 resected patients (35 per study arm), we will have 80% power to detect an increase in the 3-year OS rate from 58.8% to 88.7% using a 2.5% level one-sided log-rank test. Note that the 3-year survival rate of the vaccine treated cohort in the study by Morse et. al. was 92.5%. We will enroll 74 patients, with the expectation that about 5% of the patients will not go on to resection due to either disease progression or complications of neoadjuvant therapy[3], leaving us with approximately 70 resectable patients. If the number of unresectable patients is higher than 5%, then we will enroll up to 78 patients.

12.4 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample)	This will comprise all subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. This population should be specifically defined in the protocol.
Treated	This will comprise all subjects who have been exposed to the planned course of treatment to any extent.

12.5 Assessment of Safety

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity.

12.6 Assessment of Efficacy

All patients who receive one dose of protocol therapy and are completely resected (rendered NED) will be evaluable for assessment of efficacy.

12.7 Data Analysis Plan

A 2.5% one-sided log-rank test will be used to test the primary hypothesis. The estimation of recurrence free survival and OS will be performed by the Kaplan-Meier product limit method on all patients who undergo complete resection. Descriptive statistics for all outcome measures will be provided. To evaluate the association between variables, either chi-square test (categorical vs. categorical) or two sample t-test (categorical vs. continuous) or correlation (continuous vs.

continuous) will be used depending upon the types of variables in comparison.

12.8 Interim Analysis

The total expected number of deaths is 22 at the end of the follow-up period. A single interim analysis is planned after 14 deaths occur. The purpose of this analysis is to allow an early assessment of efficacy. We shall use a Hwang-Shih-DeCani group-sequential boundary with $\gamma = -4$, yielding an O'Brien-Fleming-like α spending function and a one-sided stopping boundary (30), We expect to spend approximately 0.0052 of the total of $\alpha = 0.025$ at the interim analysis and the remaining 0.0198 at the final analysis. Thus the p-value in the interim must be less 0.0052 to conclude that the two arms are significantly different. At the final analysis the p-value would need to be less than 0.0198 for the two arms to be significantly different.

Power calculations were carried out using Version 1.0 the "gsDesign" package in the R statistical system (R language and environment for statistical computing, R Foundation, Vienna, Austria).

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Rutgers Cancer Institute of New Jersey's DSMP.

HCRN oversight activities include:

- Review and processing all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee with guidance from Rutgers Cancer Institute of New Jersey's DSMP.

13.2 Rutgers Cancer Institute of New Jersey's Data Safety Monitoring Committee

HCRN will provide the following for review:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Rutgers Cancer Institute of New Jersey's DSMC will review study data on a quarterly basis. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Bavarian Nordic, BMS or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or another secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.
Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Bavarian Nordic, BMS, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16. REFERENCES

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APPENDIX 1: MANAGEMENT ALGORITHMS

GI Adverse Event Management Algorithm

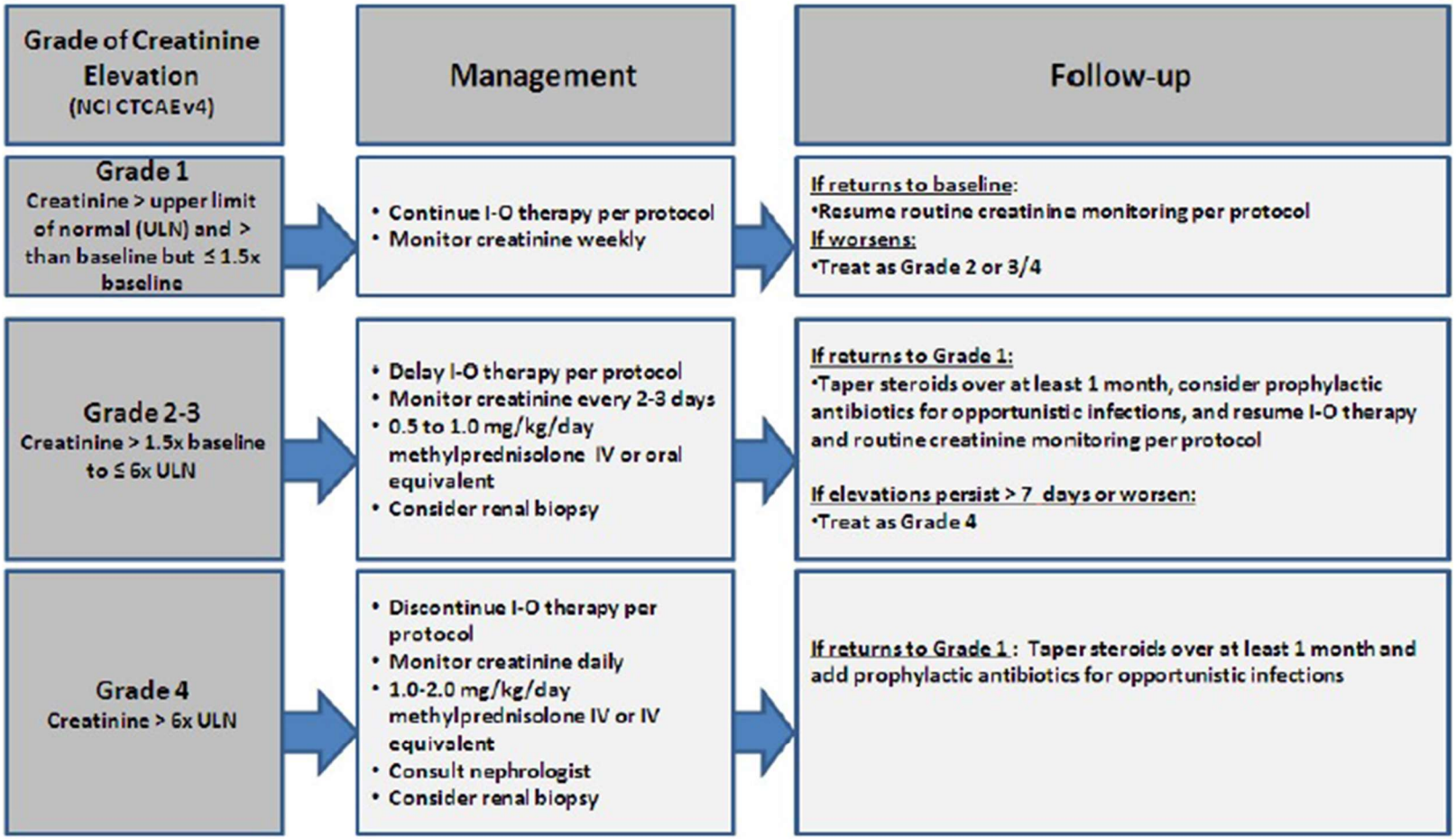
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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

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

Renal Adverse Event Management Algorithm

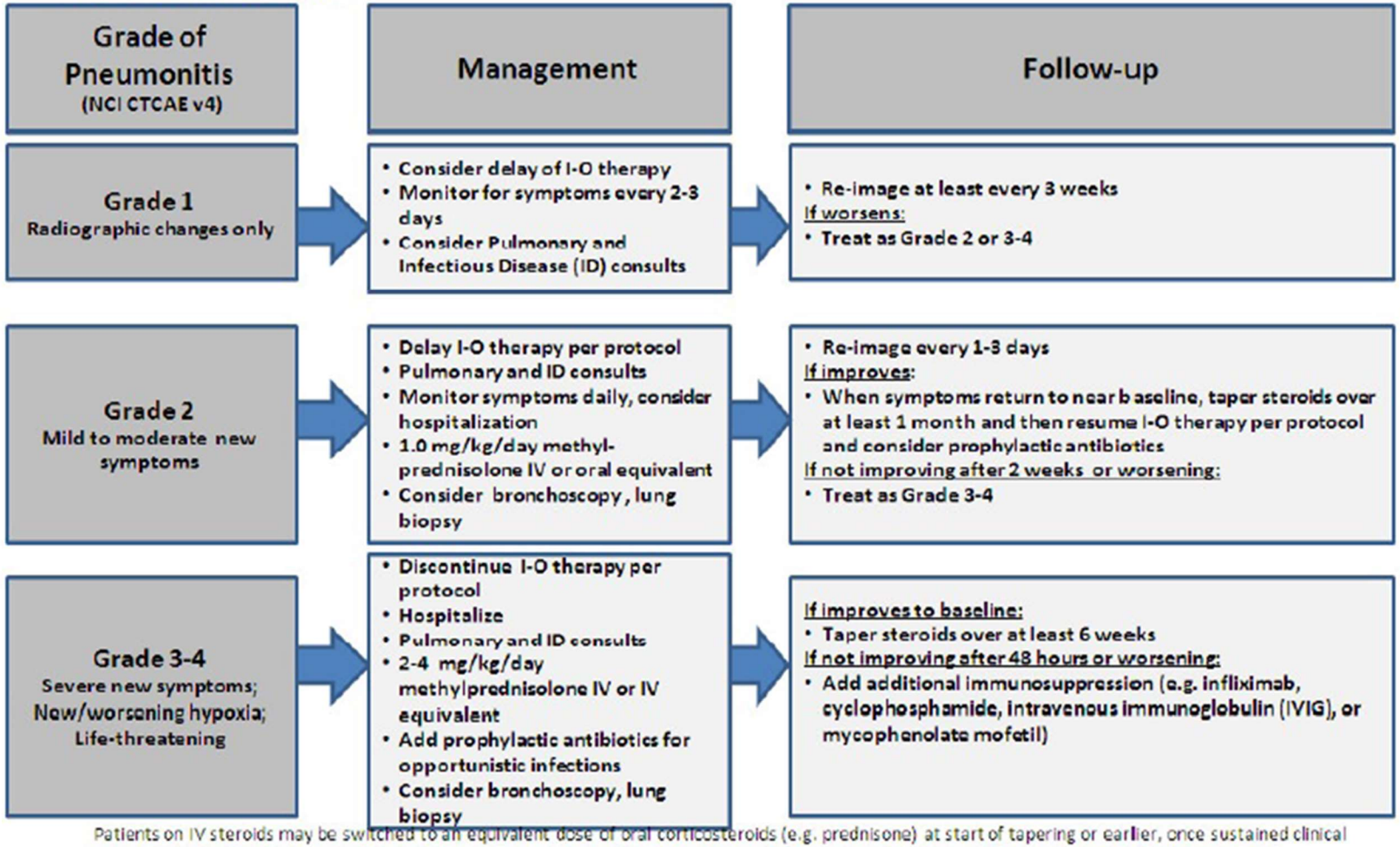
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

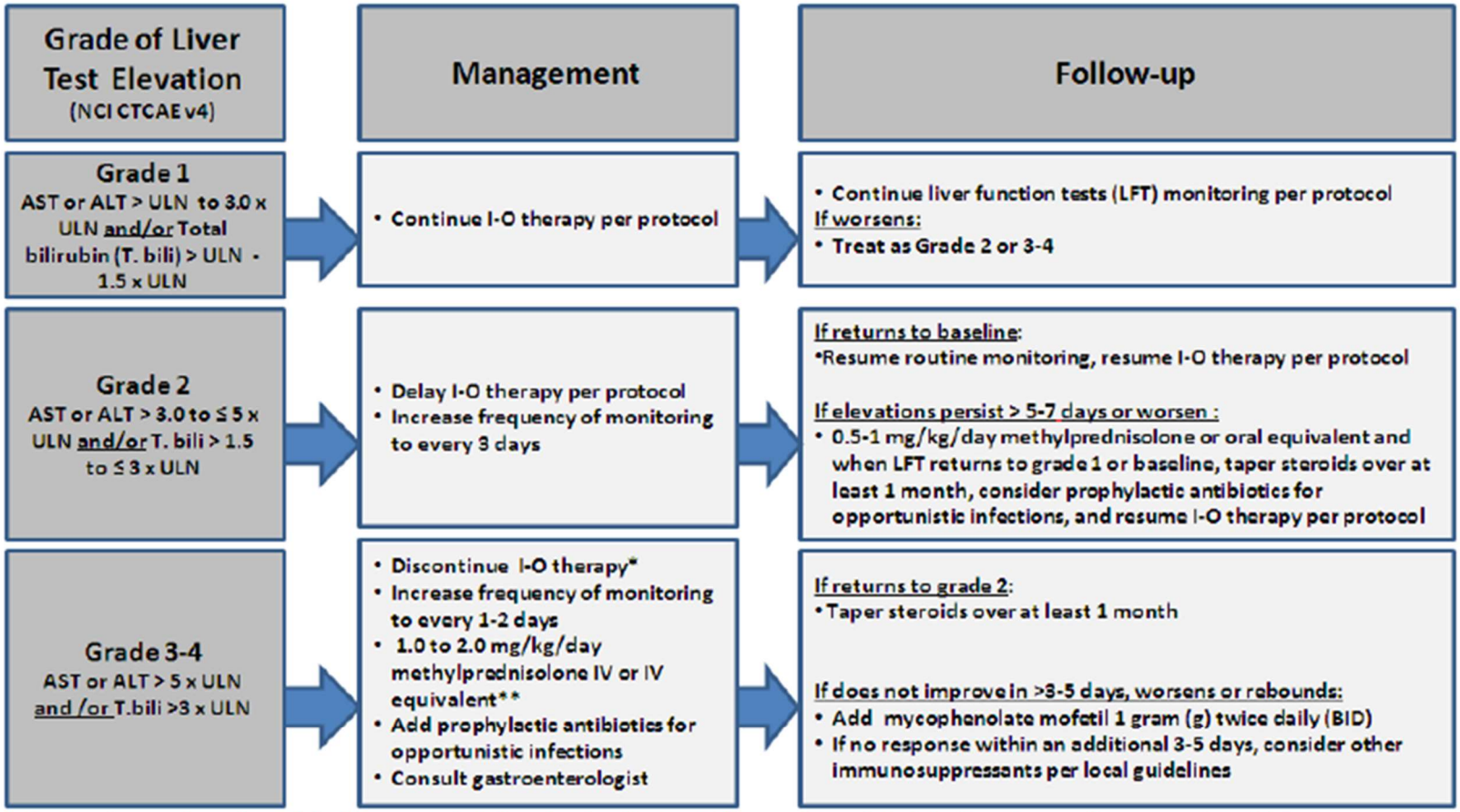
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



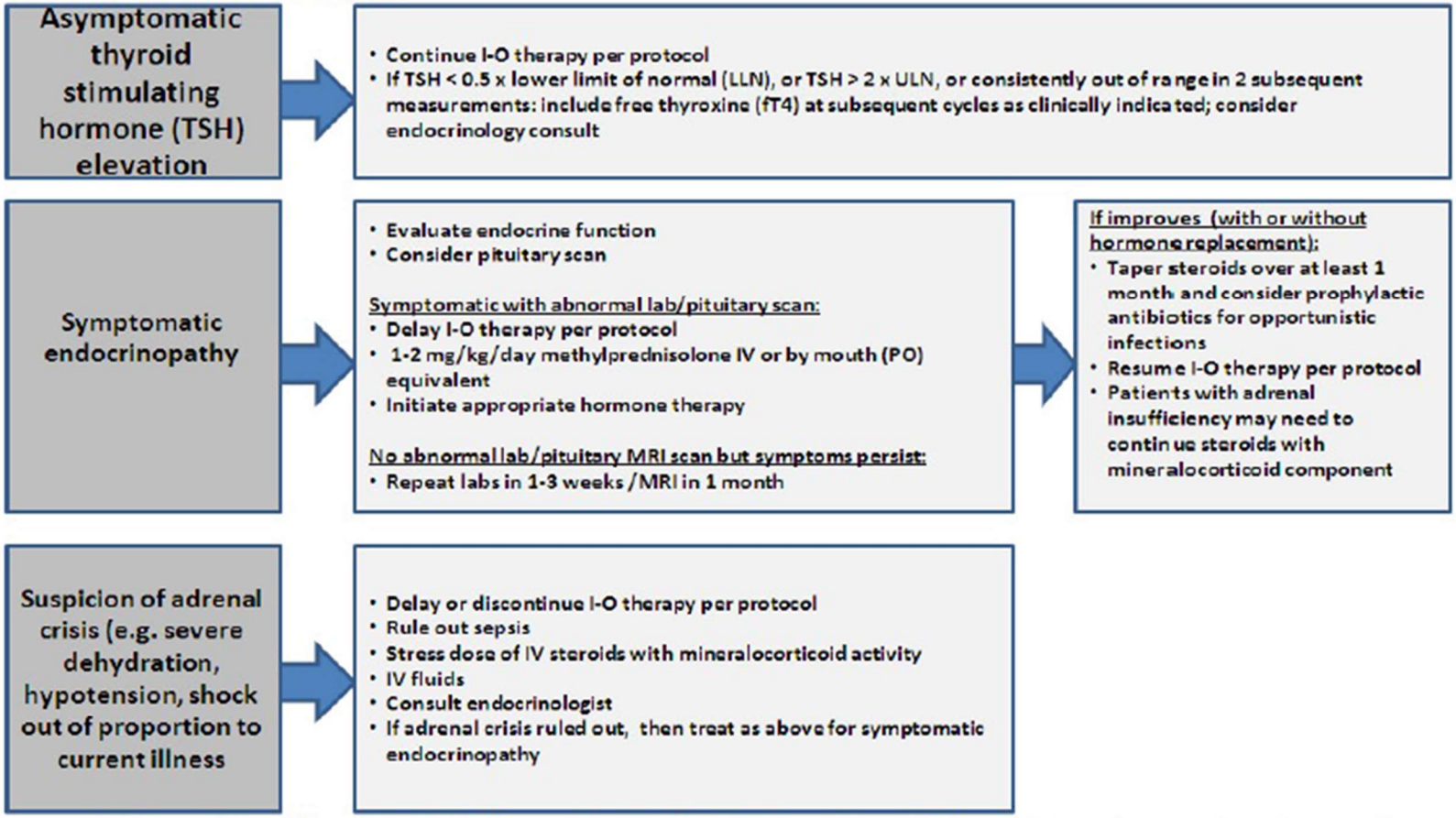
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

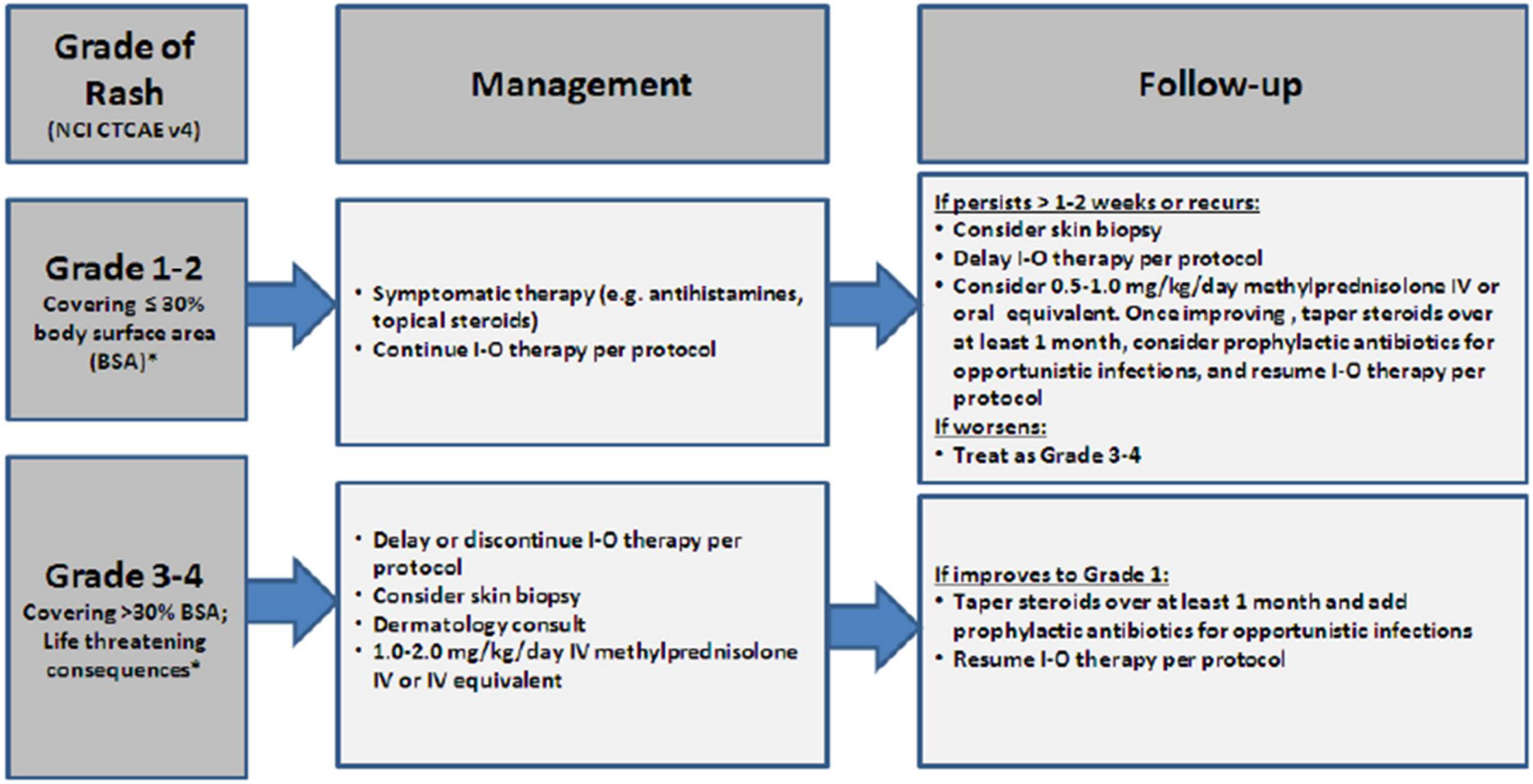
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

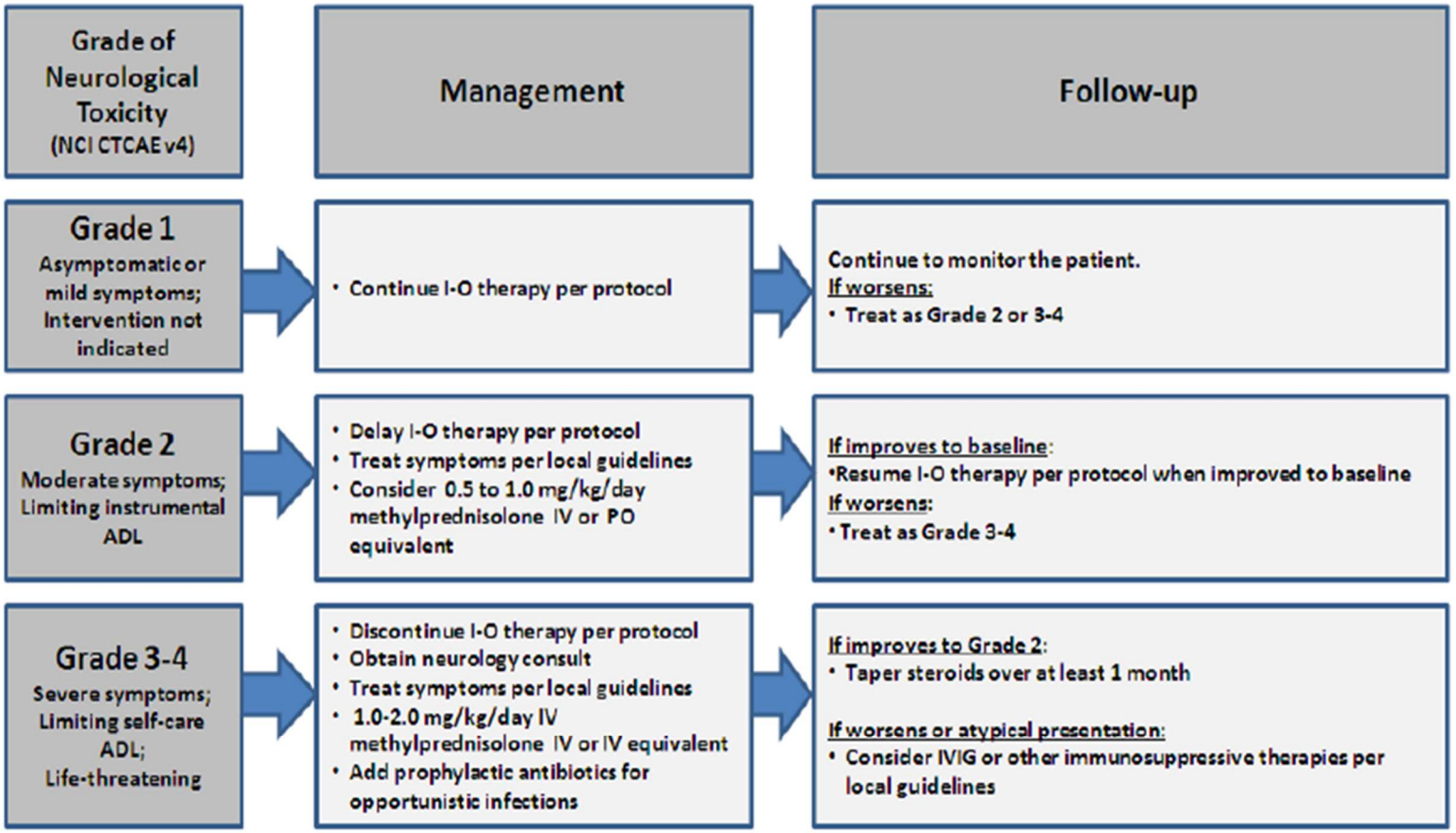
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

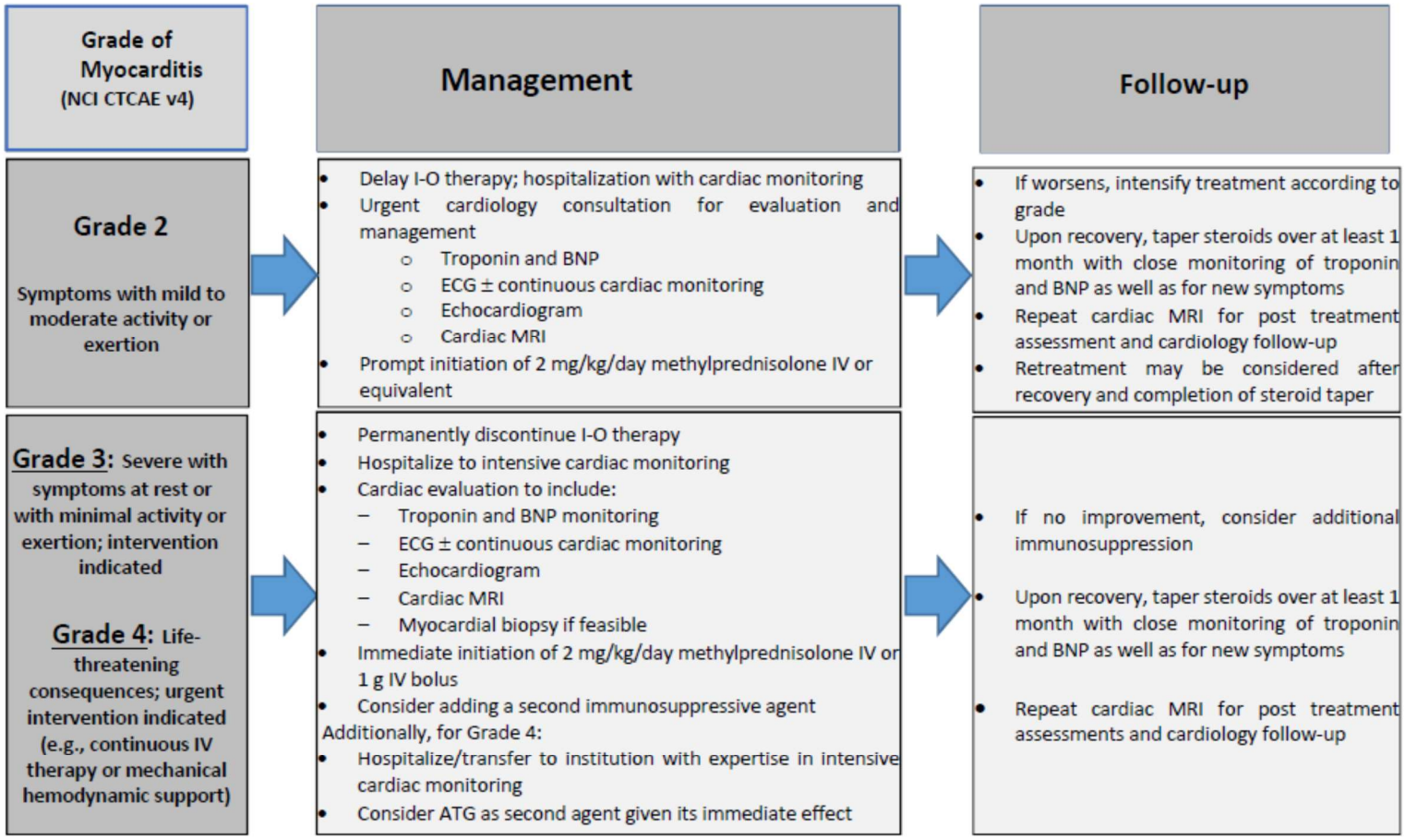
Neurological Adverse Event Management Algorithm

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



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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging