Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

A Phase II Trial of the PD-L1 Inhibitor, Durvalumab (MEDI4736) plus CV301 in Combination with Maintenance Chemotherapy for Patients with Metastatic Colorectal or Pancreatic Adenocarcinoma

Georgetown Protocol #:	2017-1189 (CRC #072016-02)
Clinicaltrials.gov #:	NCT03376659
IND #:	17698
Initial Concept Date:	Version 1.0, July 31st, 2015
Initial Protocol Version Date:	Version 1.0, November 18th, 2015
Amended:	Version 1.1, December 20th, 2015 Version 1.2, December 26th, 2015 Version 1.3, March 5th, 2016 Version 1.4, May 22nd, 2016 Version 2.0, March 10, 2017 Version 2.1, July 23rd, 2017 Version 2.2, November 11th, 2018 Version 2.3, February 12th, 2019 Version 2.4, October 1, 2019
Study Chair:	Michael J. Pishvaian, MD, PhD University of Texas, MD Anderson Cancer Center, Houston, TX
Principal Investigator:	Benjamin Weinberg, M.D. Lombardi Comprehensive Cancer Center Georgetown University Medical Center 3800 Reservoir Road, NW Washington, DC 20057 Telephone (202) 444-2223 Fax (202) 444-9429 E-Mail: Benjamin.A.Weinberg@gunet.georgetown.edu
Associate Investigator(s):	Tanios Bekaii-Saab, MD Mayo Clinic, Phoenix, AZ Bassel El'Rayes, MD Emory University
Multicenter Project Managers:	Eunice Shim, BS Nicole Swanson, BS, MFS Lombardi Comprehensive Cancer Center Georgetown University Medical Center

Collaborators:	James L. Gulley, M.D., Ph.D., F.A.C.P. Center for Cancer Research, NCI Jeffrey Schlom, Ph.D. Center for Cancer Research, NCI Chip Petricoin, PhD George Mason University Jonathan Brody, PhD Thomas Jefferson University Steve Byers, PhD Lombardi Comprehensive Cancer Center Georgetown University Medical Center
Corporate Collaborators:	Medimmune, Inc (AstraZeneca) Bavarian Nordic, Inc
Biostatistician:	Hongkun Wang, PhD Lombardi Comprehensive Cancer Center Georgetown University Medical Center
Funding Source:	Medimmune, Inc (AstraZeneca) Bavarian Nordic, Inc
Study Drugs:	Durvalumab (Medimmune/Astra Zeneca) CV301 (Bavarian Nordic)
Clinical Phase:	II
Number of Subjects:	Up to 52 Efficacy Evaluable Patients

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase II Trial of the PD-L1 Inhibitor, Durvalumab (MEDI4736) plus CV301 in Combination with Maintenance Chemotherapy for Patients with Metastatic Colorectal or Pancreatic Adenocarcinoma

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

Benjamin Weinberg, MD
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center

Date

INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: A Phase II Trial of the PD-L1 Inhibitor, Durvalumab (MEDI4736) plus CV301 in Combination with Maintenance Chemotherapy for Patients with Metastatic Colorectal or Pancreatic Adenocarcinoma

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____ _____

Benjamin Weinberg, MD Date
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center

Summary of Changes

The full protocol was first reviewed by the Georgetown Scientific Review Committee (CRC) on 07/20/2016. Since then updates and changes have been made, and summarized below (For each amendment, minor formatting, spelling and grammatical corrections, and pagination updates are not detailed below).

Version 2.0, 03/10/2017

1) The major change for this version involves the change from using PANVAC to CV301. As detailed extensively in the protocol, CV301 (made up of two poxvirus vaccines, MVA-BN-CV301 and FPV-CV301) is an "updated" version of PANVAC (made up of the vaccinia virus, PANVAC-V; and the poxvirus, PANVAC-F). The updated CV301 harbors the same vaccine antigens, but the major updated benefit is that the priming vector, MVA-BN-CV301, is a non-replicating poxvirus (unlike the priming vector of PANVAC, which is a vaccinia virus), there is a significant reduction in the risk profile. The changes are reflected throughout the protocol, but the major sections include:
    a. The protocol title throughout this protocol, and the ICF
    b. The background was modified to incorporate information about CV301
    c. Much of Section 8.2 was modified, and many of the details of CV301 preparation and safety were deferred to the CV301 Investigator's Brochure
2) The dosing/schedule for CV301 differs from PANVAC
    a. There are two priming doses now - with a CV301 prime with MVA-BN-CV301 of 1.6 x 10^9 infectious units/0.5 mL (Inf.U) given subcutaneously (s.c.) on Day 1 ***and*** Day 29.
    b. The boost with FPV-CV301, dosed at 1 × 10^9 Inf.U/0.5 mL will be given s.c. on Day 1 of Weeks 9, 13, 17, and 21 (i.e. q4 weeks x 4); and then weeks 25 and 37 (i.e. q12 weeks X 2): and then starting week 53 q24 weeks continuously. There will be no stopping or restarting of the CV301.
    c. These changes are reflected in:
        i. The Synopsis
        ii. Figures 2 and 3 and 5 and 6
        iii. Section 4.1
        iv. Tables 4 and 5
3) The schedule of the durvalumab was also clarified throughout the protocol
    a. In the synopsis
    b. Figures 2 and 3 and 5 and 6
    c. Section 4.1
    d. Table 4 and 5
4) The schedule of events was clarified throughout the protocol to define the study activities as weeks, rather than cycles. The studies activities table (Table 4) and checklist (Table 5) were also updated accordingly.
5) The IRB # was updated to reflect IRB submission in 2017 and the CRC number was added. This is reflected in the cover page and study synopsis and the informed consent
6) Changes to the cover pages were made including:
    a. Removing the Study Co-Chair and one scientific collaborator
    b. Adding a collaborator
    c. Adding Bavarian Nordic as a second funding source
    d. Adding sponsor and PI signature pages
7) The "On Study" Card in Appendix B was removed for HIPAA compliance
8) The CRC raised the following concern.

    Consider revising hepatotoxicity management. Currently states to only administer steroids when AST/ALT >10x ULN.

    In response, the management of hepatotoxicity has been adjusted (which also parallels better the NIH CTC grading) to start steroids for AST/ALT >5X ULN. Changes are reflected in:
    a. Table 7

9) The tissue utilization plan has been updated. Six cores will be requested with two samples that need to be collected as snap frozen samples; one sample now sent directly to Dr. Steve Byers at Georgetown; and one sample sent directly to Dr. Brody at Thomas Jefferson. These changes, as well as the sample labeling details, are reflected in:
    a. Section 4
    b. Section 9
    c. Appendix C
10) There have been significant safety and toxicity management updates based on the updated Investigator's brochure for Durvalumab (Version 10.0, 12 December 2016). These changes are reflected in:
    a. The background on Durvalumab, including the sections on safety and efficacy
    b. The Informed Consent Form
    c. Appendix E

Version 2.1, 07/23/2017

1) The only major change for Version 2.1, 07/23/2017, as compared to Version 2.0, 03/10/2017 is that the Investigator's Brochure for CV301 has now been updated to include the data from the Phase I trial of single agent CV301, and a Recommended Phase II Dose has now been confirmed. The dosing included in Version 2.0, 03/10/2017 as written was correct, but the provisional highlighting in that version was removed.
    a. Correspondingly, a section on the clinical experience of CV301 was added, Section 1.11.3.2.3
2) One other minor point is that the NCI will not be participating as a clinical site (only as a scientific collaborative site), and thus Austin Duffy was removed as one of the co-investigators, and the NCI was removed as a clinical study center

Version 2.2, 11/11/2018

1) Information on the cover page and synopsis page was updated
2) To clarify confusion over the details of the timing of enrollment, the inclusion criteria were updated to read:

Stable on, or responding to 1st line therapy for metastatic disease

- *Radiographically (RECIST 1.1) confirmed stable or responding disease for at least 8, and not more than 16 weeks from the initiation of 1st line therapy for metastatic disease*
- *Due to the timing of enrollment, patients who have completed a maximum of 16 weeks of 1st line chemotherapy may be enrolled >16 weeks after initiation of 1st line therapy if disease stability/response (without additional intervening therapy) can be documented within 4 weeks prior to first dose of CV301*

3) Windows of time (i.e. +/- X number of days) were added for study procedures throughout the protocol to accommodate patient schedules
4) In Section 8, the dose and schedule of treatments were clarified:
    a. The dose and schedule of the capecitabine, and the dose, infusion time, and schedule of bevacizumab were clarified
    b. It was clarified that both MVA-BN-CV301 and FPV-CV301 should each be administered as a single syringe at each dosing timepoint.
5) The order of administration of agents was added to section 4.1
6) The patient and sample labelling schema was updated (Section 4.3 and Appendix C)
7) The timing of the on treatment biopsy was corrected to Week 6 (Synopsis and Section 4.3.4 and Tables 4 and 5, and Appendix C)
8) The timing of the blood samples was pared down to before treatment and on weeks 9, 17, and 49 and at the off study visit (Synopsis and Section 4.3.4 and Tables 4 and 5, and Appendix C)
9) The details of the collection and shipping for the lab samples were deferred to the Lab Manual (Section 4, 9, and Appendix C)
10) Minor editorial/proofreading/typesetting corrections were made throughout the protocol

Version 2.3, 02/12/2019

1) Based on updated safety information, as detailed in Section 1.10.3, based on review and approval by the FDA and the Georgetown IRB, we have chosen to remove the Phase I lead in portion of the trial. Thus, this will be considered ONLY a two cohort, Phase II trial. Up to 46 efficacy evaluable patients will be enrolled (though assuming a 10% drop out rate, up to 52 patients may be enrolled).
    a. All references to Phase I have been removed
    b. All references to Phase II have been removed because the whole trial is now a Phase II trial
    c. All references to "Dose Limiting Toxicities" or "DLTs" have been removed
2) The wording on the dosing of CV301 has been clarified to remove the volume of therapy, and focus on the Infectious Units as the dose:
    a. The CV301 prime with MVA-BN-CV301 now reads as "The CV301 prime with MVA-BN-CV301 is given subcutaneously (s.c.) on Day 1 and Day 29. One dose of MVA-BN-CV301 consists of 4 injections of 4 X 10^8 Inf.U in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6 x 10^9 infectious units (Inf.U) per dose."
    b. The boost with FPV-CV301 now reads "dosed at 1 × 10^9 Inf.U will be given s.c. on Day 1 of Weeks 9, 13, 17, and 21 (i.e. q4 weeks x 4); and then weeks 25 and 37 (i.e. q12 weeks X 2): and then starting week 53 q24 weeks continuously. One dose of FPV-CV301 consists of just one injection of 1.6 X 10^9 Inf.U per 0.5mL. The vaccine will be injected subcutaneously into the thigh. "
3) Additional minor corrections have been made:
    a. The study calendar made it appear as though the pre-treatment biopsy was to be performed within 2 weeks of starting treatment Week 1. That was not the intention, and the calendar has been corrected accordingly
    b. The details of when the ECGs are obtained were clarified in Section 4.4.8 and in the Study Schedules (Tables 4 and 5)
    c. The timing of dosing of bevacizumab was clarified in Section 8
    d. Indiana University will no longer be participating in the trial and reference to the site, and associate staff have been removed accordingly
4) Investigator's Brochure for CV301 has now been updated and information about three new ongoing clinical trials with CV301 was added in Section 1.10.3.2.3.
5) Minor editorial/proofreading/typesetting corrections were made throughout the protocol

Version 2.4, 08/13/2019

1) The Georgetown Principal Investigator was updated to Benjamin Weinberg, MD throughout protocol.
2) University of Texas, MD Anderson Cancer Center was added as a site.
3) Multicenter Trial Management information and the role of the Georgetown Multicenter Project Management Office was updated throughout the Protocol.
4) References to Theradex were removed since they are not managing/auditng the trial.
5) Updated enrollment procedures and Appendix B: Patient Registration Form to be consistent with Standard Patient Registration Procedures.
6) The wording on the dosing of FPV-CV301 has been modified. Per specifications from Bavarian Nordic, (as established in the Phase I trials) the FPV-CV301 must have a titer of *at least* 1 x 10^9 Inf.U. This is given as a single injection in a volume of 0.5 mL. However, the final dose may change slightly based on the lot of vaccine produced, and the flexibility in the wording *at least* will allow for some variation with the lots.
    a. Therefore, the boost with FPV-CV301 now reads as "One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1x10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh."
    b. Prior language referring to "1.6 X 109 Inf.U" for FPVCV301 has been removed.

TABLE OF CONTENTS

FIGURES AND TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

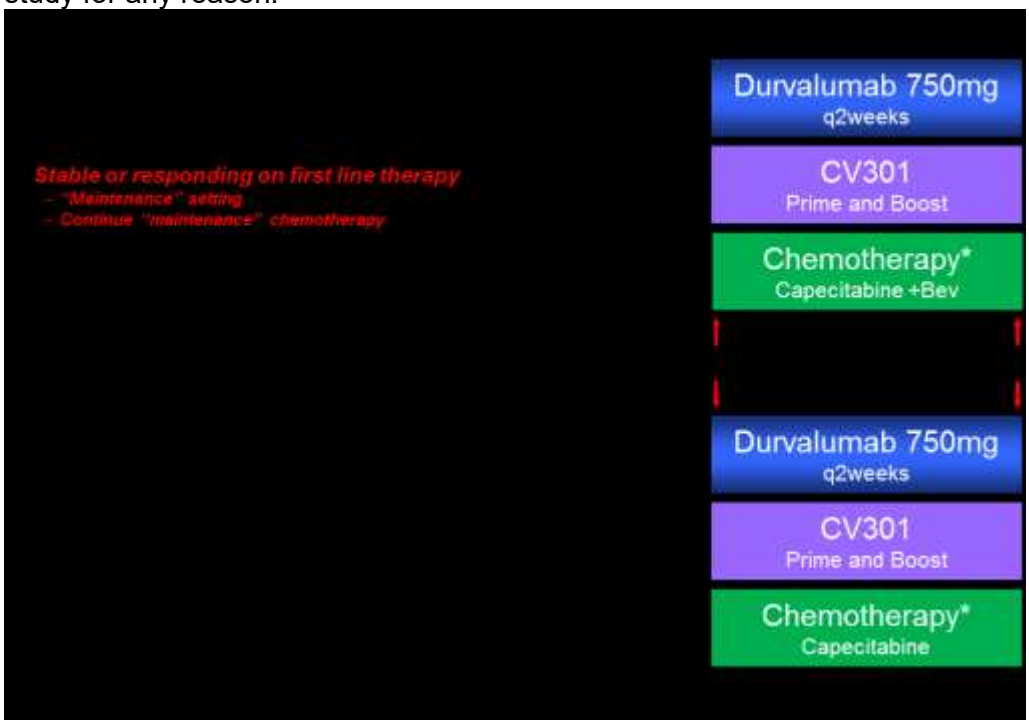
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AESI	adverse event of special interest
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALP	alkaline phosphatase
AST	Aspartate Aminotransferase
AQUA	automated quantitative analysis
APC	antigen-presenting cells
BUN	Blood Urea Nitrogen
AUC	area under the concentration-time curve
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CI	Continuous Infusion
C_{max}	peak concentration
$C_{max,ss}$	peak concentration at steady state
C_{min}	trough concentration
$C_{min,ss}$	trough concentration at steady state
CMP	Comprehensive Metabolic Panel
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
EBV	Epstein-Barr Virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FU	Fluorouracil
HIV	human immunodeficiency virus
HRPP	Human Research Protections Program
ICF	informed consent form
ICS	Intracellular Cytokine Staining
IDO	Indoleamine 2,3-dioxygenase
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1

IgG2	immunoglobulin G2
IHC	immunohistochemistry
Inf.U	infectious units
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
Mab	Monoclonal Antibody
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
ORR	Overall Response Rate; Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	programmed cell death 1
PD-L1	Programmed Cell Death Ligand 1
PD-L2	programmed cell death ligand 2
PFS	Progression Free Survival
PFS_{4mos}	Progression Free Survival Rate at 4 Months
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	QT interval on ECG corrected for heart rate
QTcF	QT interval on ECG corrected using the Fridericia's formula
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	Recommended Phase II Dose
s.c.	subcutaneous
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TAA	Tumor-associated Antigens
TCR	T-Cell Receptor
TIL	tumor infiltrating lymphocyte
T_{max}	time to peak concentration
$T_{max,ss}$	time to peak concentration at steady state
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells

STUDY SYNOPSIS

Title	A Phase II trial of the PD-L1 inhibitor, Durvalumab (MEDI4736) plus CV301 in Combination with Maintenance Chemotherapy for Patients with Metastatic Colorectal or Pancreatic Adenocarcinoma
Short Title	Durvalumab plus CV301 with Maintenance Chemotherapy
Protocol Number	2017-1189 (CRC #072016-02)
IND number and Clinicaltrials.gov number	FDA IND: 17698 Clinical Trials.gov: NCT03376659
Phase	Phase II
Methodology	Open label
Study Duration	30 – 36 months
Study Center(s)	➢ Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC ➢ Mayo Clinic, Phoenix, AZ ➢ Emory University, Atlanta, GA ➢ University of Texas, MD Anderson Cancer Center, Houston, TX
Objectives	Primary Objectives: *Colorectal Cancer (CRC) Arm* To determine the 8.5 month progression free survival rate ($PFS_{8.5mos}$) of durvalumab plus CV301 in combination with maintenance capecitabine and bevacizumab in patients with metastatic colorectal cancer, whose disease is stable on, or responding to 1st line therapy for metastatic disease *Pancreatic Cancer Arm* To determine the 4 month progression free survival rate (PFS_{4mos}) of durvalumab plus CV301 in combination with maintenance capecitabine in patients with metastatic pancreatic cancer, whose disease is stable on, or responding to 1st line therapy for metastatic disease Secondary Clinical Objectives (Both Arms): To determine, in patients treated with durvalumab plus CV301 whose disease is stable on, or responding to 1st line therapy for metastatic colorectal or pancreatic cancer: 1) Objective response rate (ORR) and duration of response 2) Progression free survival (PFS) 3) Overall survival (OS) 4) Disease control rate (DCR) (defined as ORR + rate of stable disease at 4 months) 5) Tolerability and safety of the combination Secondary Scientific Objectives (Both Arms): 1) To assess the predictive value of immune-inhibitory proteins, including PD-1, PD-L1 (B7H1), B7H3, B7H4, IDO, and arginase; and to assess the characteristics of the infiltrating T-cells in tumor samples. 2) Using a flow-based assay, to determine the number of immune cell subsets from peripheral blood mononuclear cell (PBMC) at baseline and during treatment and attempt to identify a pattern correlating with clinical benefit.

	3) To evaluate the antigen-specific T-cell activation against the target antigens of the vaccine, MUC-1 and CEA as well as other potential cascade antigens, including but not limited to brachyury. 4) To evaluate serum soluble factors and serum cytokine expression profiles at baseline and on treatment and determine correlates of clinical benefit. 5) To evaluate the relationship between tumor mutation burden and clinical benefit. 6) To evaluate the expansion of peripheral and, potentially, intratumoral T cell clones as correlates and identify correlation with clinical benefit. <u>Exploratory Scientific Objectives (Both Arms):</u> 1) To assess, in patient tumor samples, the predictive value, and the changes in response to treatment of immune-inhibitory proteins and other cell signaling pathways as measured by reverse phase phosphoprotein pathway analysis of the laser capture microdissected tumor epithelium and tumor stroma/immune cell compartments. 2) To develop *ex vivo* models of patient tumors derived from patient tumor samples
Number of Subjects	Minimum: 28 Maximum: 52 It is estimated that a total of up to 52 patients will be enrolled in the study. Specifically, a minimum of 28 patients could be enrolled in the first Simon Minimax Stage of the two Phase II portions (14 in each cohort). Each Phase II cohort will enroll a maximum of 23 evaluable patients, and allowing for a 10% dropout rate, up to 26 patients may be enrolled. Thus, the absolute minimum number of patients for the trial is 28 and the absolute maximum number of patients for the trial is 52.
Diagnosis and Main Inclusion Criteria	<u>Key Inclusion Criteria</u> 1) Histologically confirmed metastatic colorectal or pancreatic adenocarcinoma 2) Stable on, or responding to 1st line therapy for metastatic disease o Radiographically (RECIST 1.1) confirmed stable or responding disease for at least 8, and not more than 16 weeks from the initiation of 1st line therapy for metastatic disease o Due to the timing of enrollment, patients who have completed a maximum of 16 weeks of 1st line chemotherapy may be enrolled >16 weeks after initiation of 1st line therapy if disease stability/response (without additional intervening therapy) can be documented within 4 weeks prior to first dose of CV301 3) Radiographically measurable disease 4) Disease that is amenable to serial biopsies 5) Age ≥ 18 years 6) ECOG performance status 0 or 1 7) Adequate hepatic, bone marrow, and renal function. <u>Key Exclusion Criteria</u> 1) No active severe infection, or known chronic infection with HIV or hepatitis B virus 2) No cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months

	3) No women who are pregnant or breastfeeding, and no women of childbearing potential without using dual forms of effective contraception 4) Patients with known CNS metastases 5) Anticipated patient survival under 2 months
Study Design	Basic Study Design This is a dual arm, open label phase II study to evaluate the safety and clinical activity of the combination of durvalumab with CV301 in combination with maintenance chemotherapy for patients with metastatic colorectal or pancreatic cancer whose disease is stable on, or responding to 1st line therapy for metastatic disease. Patients with metastatic colorectal or pancreatic adenocarcinoma who still have an adequate performance status and normal hepatic and renal function will be eligible. The trial will consist of two parallel Phase II trials – one for patients with metastatic colorectal cancer, and one for patients with metastatic pancreatic cancer (Figure 1). Patients will be seen every two weeks through eight weeks, and then routinely every 4 weeks thereafter for as long as the patient is actively on study. Adverse events will be monitored throughout the trial (safety tests will be performed every 2 weeks for the first 8 weeks, and then every 4 weeks thereafter) and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Restaging studies will be performed every 8 weeks (+/- 5 days) (typically CT scans), by the calendar. Patients whose tumors have not progressed at the time of restaging, and who continue to tolerate treatment will continue on study. The study is estimated to last 36 months. Patient treatment will continue until disease progression, death, or until the physician or patient request removal from the study for any reason.  **Figure 1: Trial Schema**

Study Product, Dose, Route, Regimen

Please note that for all durvalumab and CV301 (and bevacizumab for the colorectal cancer patients), treatments may occur +/- 3 days to accommodate patient scheduling

Patients will begin maintenance chemotherapy beginning Week 1. This will be dosed as capecitabine 1000mg orally twice a day given Monday – Friday every week [3]. In addition colorectal cancer patients will receive maintenance bevacizumab, dosed at 5mg/kg IV q2weeks [4].

Patients first receive two priming doses with CV301 prime with MVA-BN-CV301 which is given subcutaneously (s.c.) on Day 1 and Day 29. One dose of MVA-BN-CV301 consists of 4 injections of 4 X 10^8 Infectious Units (Inf.U) in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6 x 10^9 Inf.U per dose. Then, starting week 9, patients will begin therapy with FPV-CV301. One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1x10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh on Day 1 of Weeks 9, 13, 17, and 21; and then weeks 25 and 37: and then starting week 53 q24 weeks continuously until progression.

Week 3, Day 1, patients will also begin therapy with durvalumab, which will be subsequently given every two weeks until progression (or intolerance).

Figure 2: Durvalumab plus CV301 Treatment Schedule.

Durval = durvalumab.

Duration of administration

Durvalumab and FPV-CV 301 will continue until disease progression (or intolerance). Maintenance chemotherapy (capecitabine (+ bevacizumab for CRC)) will also continue until disease progression (or intolerance). However, in the event of a complete response, patients may stop the maintenance chemotherapy and continue the durvalumab and FPV-CV301 alone after 52 weeks (one year). Patients who stop maintenance chemotherapy after 52 weeks, and whose disease then begins to progress/recur may be restarted on the maintenance chemotherapy until further disease progression.

Response Assessment

The primary efficacy objective is to determine the $PFS_{8.5mos}$ in the colorectal cancer arm, and the PFS_{4mos} in the pancreatic cancer arm. Disease response/progression will be assessed according to RECIST 1.1. However, RECIST 1.1 will be adapted to account for the potential of pseudoprogression, in which immune-mediated tumor infiltration may lead to an initial increase in the size of the tumors, and can lead to a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, standard RECIST 1.1 criteria may not provide an accurate response assessment of immunotherapeutic agents such as durvalumab and FPV-CV301. Therefore, RECIST 1.1 will be used with the following adaptations, and as detailed in Section 6 of the full protocol:

	If radiologic imaging shows initial progressive disease (PD), but patients are adequately tolerating therapy, patients may continue therapy until the next restaging while awaiting radiologic confirmation of progression. The decision to continue therapy should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria: • Absence of signs and symptoms indicating disease progression • No decline in ECOG performance status • Absence of rapid progression of disease • Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention When feasible, subjects should not be discontinued until progression is confirmed. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease: • If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy.
Multicenter Trial Management	<u>Personnel</u> At each site, personnel dedicated to this protocol will be: - A site PI - A research coordinator and data manager In addition, Georgetown University's Multicenter Project Management Office will oversee the conduct of the trial at Lombardi-Georgetown and additional sites. Georgetown University's Multicenter Project Management Office will be the main point of contact for the study chair, Dr. Pishvaian and the other site PIs for any study related concerns, including data management and regulatory. <u>Patient Enrollment</u> Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's screening number and initials, to the site PI, Dr. Pishvaian, and to Georgetown University Multicenter Project Management Office. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's Quality Assurance Office (QAO) by secure email or fax to confirm eligibility. Patients should not start therapy until Dr. Pishvaian and Georgetown University's QAO have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment. <u>Data Collection and Management</u> Patient data will be entered into the on-line accessible database (the database will be built with case report forms (CRFs) at Georgetown upon trial approval). This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to initiating any study related activities, and all ongoing patient data should be entered within one week of each patient visit.

	Trial Auditing Georgetown University's Multicenter Project Management Office will provide annual trial auditing for this study. Georgetown University's Multicenter Project Management Office will arrange all primary source documents for the patients from all sites to be audited. Auditing of the study will occur at Lombardi-Georgetown, and will be performed on a random sampling of the patients selected from any site. Conference Calls A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.
Study Product, Dose, Route, Regimen	1) MVA-BN-CV301 (prime) - two priming doses given s.c. on Day 1 and Day 29. One dose of MVA-BN-CV301 consists of 4 injections of 4 X 10^8 Inf.U in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6 x 10^9 Inf.U per dose. 2) FPV-CV301 (boost) - One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1x10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh on Day 1 of Weeks 9, 13, 17, 21, 25, 37, and q24 weeks starting week 53. 3) Durvalumab – 750mg IV q2 weeks 4) Capecitabine – 1000mg orally twice a day, Monday – Friday Weekly 5) Bevacizumab (colorectal cancer only) – 5mg/kg (Based on weight at screening unless 10% change) IV q2weeks Importantly, the dose of capecitabine parallels the dose used in the "maintenance" setting for pancreatic cancer[3]. However, for colorectal cancer, the dose of capecitabine in the CAIRO 3 trial was higher – 625mg/m^2 continuously daily [4]. In our experience, that dose given chronically can lead to significant toxicities and is not ideally suited for the "maintenance" setting.
Duration of administration	1) MVA-BN-CV301 (prime) – two doses 2) FPV-CV301 (boost) – until progression (or intolerance) 3) Durvalumab – until progression (or intolerance) 4) Capecitabine (+ bevacizumab for colorectal cancer) – until progression (unless patients achieve a CR, in which case capecitabine (+ bevacizumab for colorectal cancer) may be stopped after 52 weeks (1 year)
Reference therapy	Reference therapy For metastatic colorectal cancer, patients enrolled in the capecitabine plus bevacizumab arm of the CAIRO3 study had a median PFS of 8.5 months, which roughly translates to a $PFS_{8.5mos}$ of 50% [4]. For pancreatic cancer, there is no direct comparator, but for second-line therapy (by analogy), multiple regimens have resulted in a median PFS of 3-5 months (average of 4 months) which roughly translates to a PFS_{4mos} of 50% [5].
Statistical Design	This trial will assess the efficacy of the combination of durvalumab plus CV301 in combination with maintenance chemotherapy for patients with metastatic colorectal and pancreatic cancer whose disease is stable on or responding to 1st line therapy for metastatic disease. The trial is divided into two arms, colorectal cancer and pancreatic cancer. The median progression-free survival (PFS) reported for patients receiving capecitabine plus bevacizumab in the maintenance setting for colorectal cancer is 8.5 months [4]; for patients with metastatic pancreatic cancer, the median PFS with second-line therapy is

	around 4 months [5]. Alternatively stated, the estimated 8.5 month PFS (colorectal cancer) and the estimated 4 month PFS (pancreatic cancer) is approximately 50%. The addition of the combination of durvalumab plus CV301 to maintenance chemotherapy would be of great interest in these patient populations if it could increase the 8.5 month PFS rate (colorectal cancer) and 4 months PFS rate (pancreatic cancer) to 75% or higher. Thus, the primary endpoints of this trial are the 8.5 months PFS rate in the colorectal cancer arm, and the 4-month PFS rate in the pancreatic cancer arm. We will use a two-stage Simon Minimax Phase II design [6] in each arm. All patients meeting the eligibility criteria who have signed a consent form, begun treatment, and are not lost to follow-up or who are not taken off study for reasons other than progression or death will be considered evaluable. The statistical design for both the colorectal cancer arm and the pancreatic cancer arm is the same, despite the fact that the estimated PFS timing is different. We will assume a one-sided alpha level of 0.05 and a power of 80% to test the null hypothesis of PFS rate (at 8.5 months for colorectal cancer and 4 months for pancreatic cancer) is at most 50% vs. the alternative hypothesis of PFS rate of at least 75% for each parallel arm. In the first stage, 14 patients will be needed. If 7 or fewer of the 14 patients are alive and progression-free (at 8.5 months for colorectal cancer and 4 months for pancreatic cancer), we will conclude that this treatment is insufficiently active in this population and terminate the study. If 8 or more of these 14 patients are alive and progression-free (at 8.5 months for colorectal cancer and 4 months for pancreatic cancer), we will continue the study to the second stage and accrue a total of 23 evaluable patients. If 15 or fewer of these 23 patients are alive and progression-free (at 8.5 months for colorectal cancer and 4 months for pancreatic cancer), we will conclude that this treatment is insufficiently active in this population. If 16 or more of these 23 patients are alive and progression-free (at 8.5 months for colorectal cancer and 4 months for pancreatic cancer), this will be considered adequate evidence of efficacy of this treatment and may be recommended for further testing in subsequent studies. Assuming a drop-out rate of 10%, a total of 26 patients for each arm will be accrued. <u>Study Feasibility</u> Across our centers, more than 400 new cases of pancreatic cancer and 800 cases of colorectal cancer are seen yearly, at least half of whom have metastatic disease. Since at least 50% of patients with metastatic colon cancer and pancreatic cancer achieve stable disease on first line therapy, we anticipate that across our centers, at least 100 patients per year will be eligible for this trial. Nevertheless, given the barriers for recruiting any patient to a clinical trial, we conservatively estimate that recruitment will take 24 – 30 months. With each patient followed for a minimum of 8 weeks, the anticipated time to complete follow-up of all patients will be 30 – 36 months. The team at the NIH led by Dr. Gulley and Dr. Schlom have years to decades of experience in understanding and harnessing the immune response to cancer. They have published using the techniques proposed herein. Thus completion of the correlative studies is highly feasible.
Correlative Research	**<u>Correlative Research</u>** Serial tumor biopsies will be taken before treatment and during week 6. Blood samples will be taken before the initiation of study treatment and on weeks 9, 17, and 49, and at the off study visit. The characteristics of the tumor cells, the

tumor stroma, and of the infiltrating T-cells in the tumor samples and in the blood will be analyzed.

This trial will be conducted in conjunction with Dr. Jeffrey Schlom, Chief of the Laboratory of Tumor Immunology and Biology and Dr. James Gulley, Chief of the Genitourinary Malignancies Branch (Head, Immunotherapy Section) in the Center for Cancer Research, NCI, NIH, along Dr. Steve Byers at Georgetown, Dr. Jonathan Brody at Thomas Jefferson University, and Dr. Chip Petricoin at George Mason University.

Immune Correlates – Methodology

Tumor Immunohistochemistry Analysis

We will employ digital immunohistochemistry using MAbs against targets including CD3, CD4, CD8, PD-1, PD-L1 along with isotype control MAbs to examine the extent of immune infiltrate in any biopsies collected before treatment and during week 8 on study. If enough tissue is available, we may also stain for FoxP3, IDO, arginase, TIM3, LAG3 MHC and other markers related to immune activation and inhibition. Reverse Phase Protein Microarray analysis will also be used to quantitatively measure these proteins (CD3, CD4, CD8, PD-1, PD-L1, FoxP3, IDO, arginase, TIM3, LAG3 MHC) along with activated ZAP70, T cell receptor, JAK-STAT signaling in the laser capture microdissected stroma and tumor epithelium, when appropriate

Peripheral Blood Antigen Specific T cell Immune Response

Analysis of antigen-specific responses will be assessed by intracellular cytokine staining (ICS) following a period of in vitro stimulation with overlapping 15-mer peptide pools encoding the tumor-associated antigens (TAAs) CEA, MUC-1, and brachyury. The TAA peptide pools have been designed to contain agonist epitopes that have been previously identified [7-9]; peptide pools encoding for HLA and CEFT (a mixture of CMV, EBV, Flu, and Tetanus toxin) will serve as negative and positive controls, respectively. Peptide mixes will be purchased from JPT (Berlin, Germany), reconstituted in DMSO, and utilized immediately. Cryopreserved PBMC from patients before therapy and at specified time points will be thawed and rested overnight at 37^{o}C, 5% CO2 in complete media (IMDM supplemented with 10% Human AB, 2mM glutamine, 100 units/ml penicillin, and 100 µg/ml streptomycin). The next day (Day 0), PBMC will be seeded in 12 well plates (2.5 x106 in 1 mL), and stimulated with peptide mixes (0.1µg/mL per peptide); cultures will be supplemented on days 3 and 5 with cytokines (IL7 and IL15, 10 ng/mL, PeproTech, Rocky Hill, NJ) and fresh media, and on day 7 will be rested (with removal of cytokines and peptide). On day 11, 1x10^{6} cells will be restimulated for 24 hours in 96 well plates with peptide mixes in the presence of anti-CD107a-APC (clone H4A3, BD Biosciences); brefeldin A (1µl/mL) and monensin (0.7µl/mL) (BD Biosciences) will be added to cultures 2 hours after the start of the restimulation and incubated for the final 22 hours. PBMC will then be stained with anti-CD4-PerCP-Cy5.5 (clone OKT4, Biolegend), anti-CD8-AF700 (clone OKT8, Ebioscience), and anti-TNF-PE (clone MAb11), anti-IFNg-PE-Cy7 (clone 4SB3), and anti-IL-2-BV521 (clone 5344.111) (BD Biosciences).

For all flow cytometry experiments, at least 3x10^{5} events in the live gate will be acquired with a BD LSR-II flow cytometer equipped with a UV, violet, blue, and red laser. FCS files will be imported and analyzed with FlowJo V.9.7 for Macintosh (TreeStar, Ashland, OR). Fluorescence minus one (FMO) controls will be used for gating, and non-viable cells will be excluded. For ICS experiments, the absolute number of CD4+ or CD8+ lymphocytes producing cytokine or positive for CD107a will be calculated per 1x10^{6} cells plated at the start of the in

vitro stimulation (IVS). [10] The background signal (obtained with the HLA peptide pool), and values obtained prior to therapy will be subtracted from those obtained post-therapy. Values >250 will be scored as positive for TAA-specific immune response following therapy.

Peripheral Blood Mononuclear Cell Subset Analysis

Multicolor flow cytometry will be performed on frozen peripheral blood mononuclear cells (PBMC) as previously described [11]. Staining will be performed using 5 panels (Appendix D, table 1) to identify markers involved in PD-1 signaling (Appendix D, table 2, panel 1), CD4+ T cells, CD8+ T cells, and B cells (Appendix D, table 2, panel 2), Tregs (Appendix D, table 2, panel 3), NKs, NK-T, cDCs, and pDCs (Appendix D, table 2, panel 4), and MDSCs (Appendix D, table 2, panel 5). These panels will identify a total of 123 peripheral immune cell subsets (Appendix D, Table 3), which include 9 parental immune cell types and 114 subsets relating to maturation and function within the parental types. Optimal amounts of antibodies for staining were determined by previous titration experiments. Briefly, 1 million PBMCs per test will be incubated for 15 minutes at 4°C with 2 µL of human TruStain FcX (Biolegend, San Diego, CA) and Live Dead Fixable Stain Blue (Invitrogen, Waltham, MA). Surface antibodies will be added for 30 minutes at 4°C. Cells will then be washed, permeabilized (eBioscience, San Diego, CA), and stained with intracellular antibodies for 30 minutes at room temperature. Samples will be acquired on an LSRII flow cytometer (BD Biosciences, San Jose, CA) equipped with a UV, violet, blue, and red laser, and analyzed using FlowJo V9.7 for Macintosh (Treestar, Ashland, OR). The gating strategy will identify 123 peripheral immune cell subsets, with non-viable cells excluded, and negative gates set based on fluorescence minus one controls. All values will be reported as % of PBMCs in order to help eliminate the bias that could occur in the smaller populations with fluctuations in leukocyte subpopulations [12].

Serum Cytokine and Soluble Factor Analysis

Serum cytokines and soluble factors related to immune regulation will be analyzed using standard ELISA kits for soluble factors, as previously described [13] and cytokines (available via the Inglefield Laboratory, NCI, Frederick using the MesoScale platform (Rockville, MD), V-plex kit).

T Cell Clonal Expansion Assay

cDNA from PBMC will be amplified using locus specific primers for TCR-β. Previously described methods will be used to map the V region and identify the J region [14] and identify clonal sequences of interest. Analytics tools will be used to sort and identify clonal populations of interest in the post- versus pre-treatment samples. Correlation of expansion of a clonal TCR population post treatment will be correlated with clinical outcomes.

Measurements of Serum indoleamine 2,3-dioxygenase (IDO)

Tryptophan is catabolized by IDO to N-formylkynurenine which is rapidly converted to kynurenine. Measurement of serum levels of kynurenine and tryptophan can provide evidence of functional IDO activity. Because kynurenine can be further metabolized to downstream products, this assay is not entirely quantitative, but the ratio of tryptophan/kynurenine can provide a relative indication of IDO functional activity. Serum samples from patient taken before treatment and prior to the 2nd dosing of CV301 with durvalumab will be analyzed

for kynurenine and tryptophan levels by HPLC. HPLC will be performed according to the method described by Yong, *et al* [15].

Immunohistochemistry for Detection of IDO in Tissue Samples

Immunohistochemical staining will be performed on 10% formalin fixed, paraffin-embedded tissue sections (4µm). After deparaffinization and rehydration, the sections will be treated with 0.3% hydrogen peroxide and incubated with 10% bovine serum albumin to block nonspecific staining. The sections will be incubated for 15 minutes at 37°C with proteinase for antigen-retrieval. The sections will be incubated at room temperature with anti-IDO monoclonal antibody. The sections will then be rinsed and incubated with the biotinylated second antibody. After washing, the sections will be incubated with horseradish peroxidase-conjugated streptavidin, and finally treated with 3,3' diaminobenzidine tetrahydrochloride. The slides will counter stain with Meyer's Hematoxylin [16].

Double immunohistochemical analysis for the detection of CD3+ T-cells in the IDO-stained tissue sections will also be performed using mouse anti-CD3 monoclonal antibodies.

All these analyses will be done on samples taken before treatment and after 8 weeks on therapy with CV301 with durvalumab.

Genotyping IDO2 of Constitutional gDNA (unpublished and confidential data)

Indoleamine 2,3-dioxygenase 2 (IDO2) is a family member of IDO and related to the same pathway that is involved in an immune regulatory mechanism. Two functional IDO2 single polymorphisms (SNPs) are known to result in complete or partial inactivation (rs10109853:R248W – Catalytic inactivation, rs4503083:Y325X = stop Codon) were sequenced in 64 pancreatic tumor samples from 43 patients operated for resectable pancreatic cancer (41 PDA, 2 periampullary adenoca.). Genotypes were considered germline. Genotypes considered as resulting in complete inactivation (Y325X Homozygous, R248W homozygous) were grouped as a homozygous group, all the other genotypes were grouped as WT and/or Heterozygous. Histopathological features and overall survival (OS) were analyzed. A total of 43 pancreatic tumor patients were analyzed. Twenty-six patients (62.8%) were WT/Heterozygous homozygous and 16 patients (37.2%) were Homozygous. Patients in the homozygous group had considerably higher rates of Familial PDA (OR 15.6, 95% CI 1.7-146.4, P=0.007). These findings remained consistent in a sub-analysis for smoking status. Interestingly, the familial PDAs were limited to male patients (n/N=7/19,P=0.002). In a gender based sub-analysis (N=19), the homozygous patients retained their high proportion of familial PDAs (OR 18.0, 95% CI 1.5-216.6, P=0.02). A multivariate Cox hazard-model paradoxically indicated that patients in the homozygous group, while more prone to familial PDA, had a more favorable long term outcome than the WT/Hetero counterparts (HR 0.34, P=0.02).

Based on these data that strongly suggests that the presence of the IDO2 SNP has function, we will sequence the IDO2 gene for the presence of these SNPs from the blood from patients from this protocol. Specifically, we will determine if a correlation exists between the presence of an IDO2 SNP and patient response within this clinical trial.

Measurements of Serum arginase-1

	Arginase is a hydrolase mostly found in liver. It catalyzes the amino acid L-arginine to ornithine and urea. There are two isoforms of arginases, cytoplasmic arginase I and mitochondrial arginase II. Myeloid-derived suppressor cells (MDSC) expressing arginase I deplete L-arginine and profoundly inhibit T-cell functions. Increased levels of MDSC on cancer patients correlated with low L-arginase and high ornithine levels in plasma and T-cell dysfunction. Serum level of arginase I will be determined by two assays. (a) ELISA kit (BioVendor) using monoclonal antibody to arginase [17] and (b) The function of arginase will be determined by measuring the serum levels of L-arginase and L-ornithine by HPLC [18]. These analyses will be done on samples taken before treatment and after 8 weeks on therapy with CV301 with durvalumab. <u>Immunohistochemistry for Detection of arginase-1 in Tissue Samples</u> Four µm thick sections of the formalin-fixed paraffin-embedded tissue will be stained with polyclonal antibody against arginase I. Double immunohistochemical analysis for the detection of MDSC (CD11b+/CD14- and CD11b+/CD14+) MDSC in the arginase stained tissue sections will also be performed [19]. <u>Reverse Phase Phospoprotein MicroArray Analysis</u> The Reverse Phase Protein Microarray (RPPA) technology has been developed to address the analytical challenges of the sandwich and forward phase protein arrays (e.g. mismatch of sandwich antibody affinity, imprecision within and between analytes, and poor sensitivity). The platform has been designed to enable non-subjective, quantitative, multiplexed analysis of specific forms of cellular proteins (e.g. phosphorylated, unphosphorylated, and cleaved) from a limited amount of starting sample, such as with a fine needle aspirate or laser capture microdissected (LCM) cellular material to procure pure populations of the target cells of interest. Particularly suited for clinical tissue samples, RPPA uses a single antibody directed against the epitope of interest. A key attribute of the RPPA is the ability to quantitatively measure hundreds of signaling proteins concomitantly from only a few thousand cells, thus providing a critical means of broad-scale cell signaling analysis directly from tissue samples, cell culture models, and animal tissues from pre-clinical studies. The RPPA technology, invented in the lab of Drs. Liotta and Petricoin at George Mason University and now optimized for routine clinical sample analysis [20-27], is currently being employed within the CAP/CLIA complaint proteomics laboratory within the Center for Applied Proteomics and Molecular Medicine at George Mason University. No other technology can measure the activity of as many signaling proteins at once from such small amounts of input material. <u>*Ex Vivo* Models of Patient Tumors</u> Several models of *ex vivo* tumor propagation are currently being explored, including organoids and zebrafish avatars. Pre-treatment tumor samples will be used to develop an *ex vivo* model from each individual patient.

1. BACKGROUND AND RATIONALE

1.1. An Unmet Need in Advanced GI cancers

We have made significant advancements in the treatment of advanced gastrointestinal cancers over the last two decades. Patients with metastatic colon cancer are now living, on average over 30 months; while in pancreatic cancer, new combinations are leading to median overall survivals that for the first time ever are approaching 12 months. But to achieve these gains, patients must be exposed to chemotherapy continuously; and despite these gains, over 100,000 patients in the United States die each year as a result of advanced GI cancers [28]. Thus, novel therapies, particularly those with minimal toxicities are desperately needed. An immune-based approach to treating colorectal and pancreatic cancer may provide a mechanism to fight cancer with a novel approach, with the aim of extending survival but with fewer toxicities than chemotherapy. CV301 is capable of inducing a tumor-specific T-cell response against antigens significantly expressed in colorectal and pancreatic adenocarcinomas. There is great potential for synergistic anti-tumor activity with the combination of CV301 and an immune checkpoint inhibitor, allowing possible anti-tumor responses together that each agent alone could not provide.

1.2. Maintenance Therapy in Colorectal Cancer

Combination chemotherapy (e.g. FOLFOX or FOLFIRI) typically with anti-VEGF or anti-EGFR monoclonal antibodies have improved survival to 30+ months in patients with newly diagnosed metastatic colorectal cancer [29, 30]. Moreover, in patients for whom chemotherapy has led to a control of their disease, manifest as either stable disease, or a response, transitioning to “maintenance” therapy with 5FU/Capecitabine and bevacizumab improves progression-free AND overall survival compared to no chemotherapy (i.e. compared to a chemotherapy free holiday) [31]. In the CAIRO-3 trial, the median progression-free survival for patients receiving 5FU and bevacizumab was 8.5 months, compared with 4.1 months for patients who received placebo [4].

1.3. Second Line Therapy in Pancreatic Cancer

Significant improvements have also been made in just the last few years for patients with metastatic pancreatic cancer. In 2011, the combination of 5-FU, oxaliplatin and irinotecan (FOLFIRINOX) was compared against gemcitabine in a phase III trial with promising results, and FOLFIRINOX is considered the standard first-line treatment option in patients with a good performance status (PS 0-1). [32] The median overall survival (mOS) was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group. The mPFS was 6.4 months in the FOLFIRINOX group as compared with 3.3 months in the gemcitabine group. More recently, in 2013, in a Phase III trial, the combination of gemcitabine and nab-paclitaxel was also demonstrated to be superior over gemcitabine alone. [33] The median overall survival of gemcitabine + nab-paclitaxel was 8.5 months, which was statistically superior to the 6.7-month survival seen with single agent gemcitabine. The mPFS was 5.5 months in the gemcitabine plus nab-paclitaxel group as compared with 3.7 months in the gemcitabine group.

Nevertheless, the progression-free survival times in patients with metastatic pancreatic cancer have been too short to effectively pursue the concept of “maintenance” therapy. But as patients are living longer, the prospect of continuing chemotherapy with a fair degree of toxicity becomes unappealing, and a therapy that could control the disease, with little toxicity could be very appealing. The only comparator for efficacy would be for second-line therapy, and the median progression-free survival time for several Phase II second line trials ranges from 2.5 to 5.7 months (typically around 4 months) [5].

1.4. Checkpoint Inhibitors

Anti-tumor immune activation requires a variety of immunomodulatory signals, and both costimulatory and coinhibitory signals are needed to orchestrate an optimal antigen-specific immune response. Tumors can evade immune detection by expressing the programmed cell death ligand 1 (PD-L1). Blockade of PD-L1 may help overcome immunosuppressive effects and restore T-cell activity against tumors. [34-39] PD-L1 is found on the surface of many cancer cells and impairs the immune system’s

ability to fight cancer. As the T cells come close to the tumor, they are engaged by PD-L1, which starts a signal inside the T-cell that blocks the T-cell's ability to kill the cancer cell. Inhibition of PD-L1 has been shown to produce durable antitumor activity as a single agent and in combination with other therapies. However, not all patients treated respond to anti-PD-L1 therapy alone, prompting the suggestion that induction of an immune stimulatory response is required in conjunction with blockade of the inhibitory signals to illicit robust anti-tumor activity. Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. PD-L1 is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung [40], renal [41-43], pancreatic [44-46], ovarian cancer [47], and hematologic malignancies [48, 49] tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell [50, 51]. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination [52].

1.5. CV301 [53]

Garnett, et al discuss that stimulation and activation of T-cells is essential for a successful adaptive immune response to an antigen [54]; a sufficient immune response to a tumor associated antigen (TAA), such as CEA, may result in direct attack of the tumor. The carcinoembryonic antigen (CEA) is an oncofetal antigen that is expressed at high levels in most colorectal and pancreatic carcinomas. The mucin, MUC-1, is a highly glycosylated protein that is also overexpressed in many adenocarcinomas, including those of colorectal and pancreatic origin. T-cells from normal donors and cancer patients have been shown to recognize HLA-restricted epitopes derived from CEA and non-HLA-restricted epitopes encoded by MUC-1 [55, 56]. Targeting two distinct tumor antigens in a single vaccine may induce better anti-tumor effects because the generation of polyclonal T-cell responses may prevent tumor escape through antigen loss.

CV301 comprises 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 proposed 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 consists of the same five transgenes as the earlier poxviral vaccine known as PANVAC, which was the subject of two Investigational New Drug Application (IND) clinical development programs. As

such, much of the nonclinical and clinical data for PANVAC are supportive of CV301. A summary of these results are provided below.

1.5.1 PANVAC

Vaccinia vector expressing CEA, MUC-1, and TRICOM® (TRIad of COstimulatory Molecules; a vaccine containing three costimulatory molecules: B7.1, ICAM-1 and LFA-3) was named PANVAC-V, and fowlpox vector expressing CEA, MUC-1, TRICOM was named PANVAC-F [1, 57]. In the initial Phase I study using PANVAC in patients with advanced pancreatic cancer, ten patients received priming with PANVAC-V followed by three booster vaccinations with PANVAC-F. GM-CSF (granulocyte-macrophage colony-stimulating factor) was also used as a local adjuvant after each vaccination and for 3 consecutive days thereafter. Monthly booster was given if a patient had no disease progression. There was no significant toxicity; the majority of side effects were low grade injection site reactions or constitutional symptoms. Anti-CEA specific antibody was detected in 50% of patients and a heightened antigen-specific T-cell response was observed in 63% of patients [57]. The PANVAC recombinant vaccinia expresses 2 TAAs: CEA and MUC-1. For those patients who had an anti-TAA specific response, a significant increase in overall survival was noted compared with those who did not have such a response. A randomized Phase II trial was conducted in patients with colorectal cancer with completely resected hepatic or pulmonary metastases [58]. Seventy-four patients received adjuvant vaccine therapy comprising PANVAC-V and PANVAC-F, administered with autologous dendritic cells (Arm 1) or with sargramostim (GM-CSF) (Arm 2). The recurrence-free survival at 2 years was similar in the two arms, at an impressive rate of ~50% for both (47% and 55% for PANVAC with dendritic cells and PANVAC/GM-CSF, respectively). The rate and magnitude of T-cell responses against CEA was statistically similar between study arms. As a group, vaccinated patients had superior survival compared with a contemporary group of patients with metastatic colorectal cancer who had undergone resection of metastases, but who had not received adjuvant vaccine therapy [58].

1.5.2 CV301

CV301 is composed of two new constructs that were generated to replace the former PANVAC (PANVAC-V and PANVAC-F). For CV301, MVA-BN-CV301 replaced PANVAC-V, and FPV-CV301 replaced PANVAC-F. These constructs are designed to express the same five transgenes with similar expression profiles as the previous PANVAC vectors but using the non-replicating MVA-BN® vector instead of a replicating vaccinia virus vector as priming vaccine. Furthermore, changes were made to increase the genetic stability of the inserted transgenes to enhance manufacturability. The new constructs encode each of the transgenes (CEA, MUC-1, B7.1, ICAM-1 and LFA-3) with amino acid sequences that are identical to the original vectors, except for MUC-1 where additional agonistic epitopes are included. Additionally, changes were made to the DNA sequences of MUC-1, CEA, B7.1, ICAM-1 and LFA-3 to reduce homologies and optimize codon expression.

As CV301 consists of the same five transgenes as the earlier generation PANVAC, the CV301 IB relies on the available data for CV301 and the extensive nonclinical and clinical data that exists for PANVAC. However, safety data with the use of CV301 has been updated, as detailed below

1.5.3 PANVAC/CV301 plus Checkpoint Inhibitors

A clinical trial of single agent PANVAC in patients with pancreatic cancer was a negative trial, and did not improve survival compared to placebo alone [59]. Additionally, in multiple ongoing, and recently completed trials of anti-PD-1/PD-L1 therapies, there have been no consistent responses induced by single agent therapy [37]. However, mechanistically, there is great promise, as described above in the combination of a vaccine therapy with an immune checkpoint inhibitor.

The combination of a vaccine and an immune checkpoint inhibitor appears to be safe, as demonstrated by a study in which patients received a similar pox-viral vector platform incorporating multiple costimulatory molecules (TRICOM) in combination with an immune checkpoint inhibitor. Results of that study suggested that there was no obvious increase in adverse events over that

expected with immune checkpoint inhibitor alone [60]. To our knowledge, there has been no study to date combining CV301 with an immune check point inhibitor. The safety of this combination will be evaluated in the phase I part of the protocol.

1.6. Evaluation of Benefit in the Maintenance Setting

The choice to explore the benefits of the combination of durvalumab and CV301 in the maintenance setting is intended to balance several key factors. While there is great theoretical promise with this combination, there is no guarantee of benefit, and there is concern about offering this combination to patients who are in desperate need of additional treatment in the face of progressing disease. In fact, patients whose disease progresses despite this immunotherapy approach would have the opportunity to restart the first line chemotherapy that was providing benefit prior to enrollment. Moreover, understanding the effects on the immune response in tumors is a critical part of this trial – so enrolling patients whose performance status enables serial correlative marker assessment is also critical.

1.7. Immune Checkpoint Inhibitors plus Chemotherapy

There is now a vastly growing body of data demonstrating the safety and efficacy of the combination of immune checkpoint inhibitors plus chemotherapy. Most relevant to the current study, Georgetown University has been one of the lead accruing institutions for an ongoing trial of MPDL3280A (Anti-PD-L1) in combination with bevacizumab and/or FOLFOX (5-FU and oxaliplatin) in patients with metastatic colorectal cancer [61]. This trial demonstrated no safety signal of concern over the addition of MPDL3280A in combination with chemotherapy AND bevacizumab, and in fact, as part of this trial, patients who stopped oxaliplatin (after a maximum of 8 doses), were allowed to continue on maintenance capecitabine and bevacizumab (exactly paralleling the current proposal). Multiple ongoing trials with other immune checkpoint inhibitors, including durvalumab, nivolumab and pembrolizumab in combination with chemotherapy or targeted agents have repeatedly demonstrated no additional safety concerns above and beyond that seen with either the immune checkpoint inhibitors or the chemotherapy/targeted therapy alone

Combining anti-PD-L1 with standard of care provides multiple advantages that may allow for improved clinical outcomes compared with either agent alone. 5-FU and oxaliplatin have been identified as agents which can induced immunogenic cell death and/or decrease the number of regulatory T cells [62], which increases T cell activation via immunogenic cell death and antigen presentation on tumor cells resulting in increased T cell mediated killing of tumor cells. Immunogenic cell death induced by oxaliplatin is known to be capable of inducing an anti-tumor immune response [63-67]. There is also evidence that immunotherapy in combination with 5-FU is capable of increasing the immune response against tumor cells.

T cell activation and resultant production of IFN-gamma and type 1 cytokines results in PD-L1 induction in the tumor tissue. PD-L1 expression has been correlated with the likelihood of PD-1 – PD-L1 blockade to induce anti-tumor immune response and cause tumor volume reduction and clinical benefit.
Another mechanism by which the underlying anti-tumor immune response may be improved when patients are exposed to the standard of care regimen is through a process known as immunogenic modulation. Hodge and colleagues in the LTIB have demonstrated immunogenic modulation resulting in upregulation of MHC, tumor associated antigens, and FAS resulting in T cell mediated killing with chemotherapeutics, including 5-FU and oxaliplatin [68, 69].

Finally, the decreased tumor burden induced by standard of care therapy may allow better immune response by debulking the tumor and improving the microenvironment for immunologic killing [70-75]. The addition of standard of care therapy also provides ample time for an immune response to occur, which may be important considering the occasional delayed responses and prolonged stable disease findings that have been described with anti-PD-1 and anti-PD-L1 targeting agents. Given the findings with ipilimumab improving overall survival while not necessarily improving PFS [76], it may be that delayed immunologic effects create long term clinical benefit in some populations despite lack of

immediate tumor volume reduction. By using a therapy in combination with standard agents known to induce tumor volume reduction, we may be able to capture that long term benefit.

1.8. Vaccines plus Chemotherapy

To our knowledge, there have been no published reports of the combination of CV301 plus chemotherapy. But several clinical trials have demonstrated the safety of combining a vaccine plus chemotherapy. Most notably, GVAX (a "vaccine" consisting of irradiated, GM-CSF-secreting allogeneic pancreatic cell lines given intradermally to elicit a broad antigenic response) has been combined with safely with FOLFIRINOX in patients with pancreatic cancer(NCT01595321). This trial has not been published, but in personal communication with the Principal Investigator, there have been no signals of safety concerns of the combination. In addition, the yeast vaccine GI-4000 has been safely combined with gemcitabine in pancreatic cancer(NCT00300950), and with FOLFOX/FOLFIRI plus bevacizumab in colorectal cancer (NCT01322815) without safety concerns.

1.9. Enhanced Immunogenicity with Bevacizumab

Preclinical evidence indicates that vascular endothelial growth factor (VEGF) signaling in the tumor microenvironment causes disorganized perfusion, resulting in poor T cell trafficking to the tumor site, increased hypoxia, and an immunosuppressive microenvironment. Rakesh Jain's group has demonstrated significant improvement in T cell infiltration with the addition of VEGF inhibition in preclinical models [77]. In this study, VEGF inhibition increased the efficacy of a vaccine to induce T cell infiltration into the tumor, resulting in better anti-tumor effect. Similarly, Dr. Hwu's group has found VEFG blockade to result in greater T cell infiltration in adoptively transferred T cells in a murine model [78]. Alfaro, et al., found VEGF inhibition to be valuable for dendtritic cell differentiation and T cell activation [79]. Taken together, these data indicate a potential synergy between VEGF inhibition and immunotherapy, supportive of combining these agents in patients.

1.10. Study Agent(s) Background and Associated Toxicities

1.10.1. Capecitabine (Package insert) [80]

5-Fluorouracil (5-FU) is an inactive agent in its parent form, and requires intracellular activation for its anti-cancer effects. In the cell, thymidine phosphorylase converts 5-FU to FUDR, which is then phosphorylated by thymidine kinase to generate the active metabolite, FdUMP which then covalently binds to and inhibits thymidylate synthase, leading to a depletion of dTTP and preventing DNA synthesis and repair. A metabolite, FUTP is also generated, interfering with RNA synthesis as well. The most common mechanism of resistance to 5-FU is overexpression of or mutation in the thymidylate synthase gene. 5-FU is administered intravenously, and metabolism is rapid, with a half-life of only minutes, for the parent compound.

Oral capecitabine is a 5-FU prodrug that is highly bioavailable. It undergoes successive transformation to its active metabolite, 5-FU. Conversion begins in the liver, but the final step is mediated in cells by thymidine phosphorylase. Of great importance, thymidine phosphorylase is expressed at much higher levels in tumor tissues, making capecitabine much more tumor specific. Peak levels of capecitabine occur 2 hours after ingestion, and elimination is primarily through the kidneys.

Toxicities of 5-FU/capecitabine are dependent upon the dose, and also the route and schedule of administration. IV 5-FU can be given as a rapid bolus, or as a continuous infusion. Bolus administration is more associated with myelosuppression while continuous infusion and oral capecitabine are more associated with the development of hand-foot syndrome. Both routes can lead to nausea, vomiting, diarrhea, mucositis, fatigue, and rarely coronary vasospasm.

1.10.2. Bevacizumab (Package Insert) [81]

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) and prevents binding of VEGF to its receptor (VEGF-R). This prevents activation of a key pathway involved in the angiogenesis tumors require for establishing a blood supply to sustain further growth. Bevacizumab is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy. bevacizumab is dosed at 5mg/kg every two weeks.

1.10.3. CV301 Background [53]

1.10.3.1. Summary of Non-clinical Experience

CV301 comprises 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 proposed 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 consists of the same five transgenes as the earlier poxviral vaccine known as PANVAC, which was the subject of two Investigational New Drug Application (IND) clinical development programs. As such, much of the nonclinical and clinical data for PANVAC are supportive of CV301.

In vitro studies demonstrated that antigen-presenting cells incubated with PANVAC led to the activation of CEA and MUC-1 specific cytotoxic T cells that likely target tumor cells overexpressing CEA and/or MUC-1. The responses were optimal when the 3 costimulatory molecules of TRICOM were co-expressed. Humoral and cellular responses specific to CEA have also been demonstrated in mice.

It was hypothesized that poxvirus-based active immunotherapy could provide even greater improvements to patient outcome when used in combination with immune checkpoint inhibitors (ICIs) by reactivating functionally inhibited tumor-specific T cells and inducing new productive tumor-specific responses. Thus, a nonclinical proof-of-principle combination therapy study with anti-PD-1 was performed using a precursor to MVA-BN-CV301. Antitumor efficacy of poxvirus-based immunotherapy was significantly improved when combined with monoclonal antibodies that block the activity of PD-1, and worked through different (and complementary) mechanisms of action. Therefore, combination therapy of reduced-dose ICIs with poxvirus-based active immunotherapy showed improved benefit in preclinical models over ICI therapy alone.

1.10.3.2. Summary of Clinical Experience

Four clinical trials with CV301 are currently ongoing, with updated details presented in section 1.10.3.2.3 below.

To date, CV301's predecessor product PANVAC has been evaluated in approximately 300 subjects (138 subjects in the clinical trials sponsored by Therion and 164 subjects in the National Cancer Institute (NCI) -sponsored trials) in the following 7 clinical trials:

• TBC-PAN-002 (completed): Phase 1, single-arm, clinical trial of PANVAC in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) in subjects with unresectable adenocarcinoma of the pancreas

• TBC-PAN-003 (completed): Phase 3, 2-arm, clinical trial of PANVAC in combination with GM-CSF versus best supportive care or palliative chemotherapy in subjects with metastatic (Stage IV) adenocarcinoma of the pancreas who have failed a gemcitabine-containing chemotherapy regimen

• CTEP No. 6536 (completed): Phase 1, 4-arm, clinical trial of PANVAC in combination with GM-CSF in subjects with metastatic colorectal, non-colorectal, breast, or ovarian cancer

• CTEP No. 7606 (ongoing; enrollment and treatment phase completed): Phase 1, single-arm, clinical trial of PANVAC in combination with GM-CSF in subjects with incurable pancreatic cancer

• CTEP No. 6977 (completed): Phase 2, 2-arm, clinical trial of PANVAC + docetaxel compared with docetaxel alone in subjects with metastatic breast cancer

• CTEP No. 8087 (completed): Phase 2, 2-arm, clinical trial of DCs + PANVAC compared with GM-CSF + PANVAC in subjects with hepatic or pulmonary metastases secondary to adenocarcinoma of the colon and rectum

• CTEP No. 9539 (ongoing): Phase 2, 2-arm, clinical trial of PANVAC + Bacillus Calmette-Guerin (BCG) compared with BCG alone in subjects with high grade non-muscle invasive bladder cancer (NMIBC) who failed at least 1 induction course of BCG

1.10.3.2.1. Safety

CV301 will be administered in a heterologous prime-boost regimen consisting of recombinant MVA-BN-CV301 followed by recombinant FPV-CV301. Since the vaccine constructs encode the same five transgenes as the earlier generation PANVAC, but using non-replicating MVA-BN as priming vector instead of replicating vaccinia virus, the proposed development program for CV301 is supported by existing nonclinical data for PANVAC.

The pilot study 6536 "An Open-Label Pilot Study to Evaluate the Safety and Tolerability of PANVAC™-V (Vaccinia) and PANVAC™-F (Fowlpox) in Combination with Sargramostim in Adults with Metastatic Carcinoma," was closed to accrual as of 5/27/2008. As of May 2013, 51 patients have been treated and the highest grade, therapy-related AEs reported are two instances of grade 3 syncope (fainting). Grade 1 or 2 injection site reaction/extravasation changes, flu-like symptoms, fever, and fatigue have been the most commonly reported events.

The phase 1 study 7606, "Immunotherapy for Unresectable Pancreas Cancer: A Phase 1 Study of Intratumoral Recombinant Fowlpox PANVAC (PANVACTM-F) Plus Subcutaneous Recombinant Vaccinia PANVAC (PANVACTM-V), PANVACTM-F and Recombinant Granulocyte-Macrophage Colony Stimulating Factor (rH-GM-CSF)," was closed to accrual and treatment on 4/20/2013. As of May 2013, 14 patients have been treated on this trial. Two grade 4 therapy-related AEs included increased lipase and increased serum amylase. Six grade 3 therapy-related AEs included colitis,

diarrhea, pancreatitis, increased lipase, and decreased lymphocyte count. Injection site reaction was the most frequently reported therapy related AE (all grade 1).

The phase 2 pilot study 6977, "Randomized Pilot Phase II Study of Docetaxel Alone or in Combination with PANVAC™-V (Vaccinia) and PANVAC™-F (Fowlpox) in Adults with Metastatic Breast Cancer," was closed to accrual and treatment on 2/4/2013. No grade 5 therapy-related events have been reported for this study. Grade 4 therapy-related AEs included pericardial effusion, pleural effusion and a thromboembolic event. Grade 3 therapy-related AEs included decreased neutrophils, lymphopenia, leukopenia, increased alanine aminotransferase, abdominal pain, dyspnea, and injection site reaction. Injection site reaction, leukopenia, and fatigue were the most commonly reported therapy-related AEs (grades 1-3).

PANVAC has been well-tolerated in all clinical trials. The most frequent treatment-related adverse events (AEs) were injection site reaction, myalgia, fatigue, vomiting, nausea, and abdominal pain. Most treatment-related AEs were Grade 1 or 2 in severity. Serious adverse events (SAEs) related to study treatment, discontinuations due to AE, and deaths related to study treatment were rare (only 1 death due to Grade 5 pulmonary infiltrate was assessed as possibly related to study drug).

1.10.3.2.2. Efficacy

Early nonclinical studies demonstrated CV301's safety, along with its ability to activate antigen-specific T-cell responses. Murine (mu) dendritic cells (DCs) infected with rVmuTRICOMTM or rF-muTRICOMTM were shown to significantly enhance naive T-cell, allogenic T-cell, and peptide-specific T-cell proliferation in vitro. Following weekly vaccination for 4 weeks with rV-muCEA/TRICOMTM plus murine granulocyte-macrophage colony-stimulating factor (muGM-CSF) and interleukin (IL)-2, 9 of 16 treated CEA-transgenic (Tg) mice with established CEA-positive hepatic carcinoma metastases mice, remained alive through 25 weeks. By contrast, in the control group (which received non-rV plus cytokines), only 1 of 19 (5%) survived past 16 weeks.

Successful protection by vaccines comprised of combinations of costimulatory molecules was evaluated. C57BL/6 mice were vaccinated subcutaneously (SC) with either rV-CEA or rV-CEA/muTRICOM^{TM}, then challenged 100 days later with MC-38 colon carcinoma cells. All mice vaccinated with rV-CEA succumbed to tumors while all mice vaccinated with rV-CEA/muTRICOM^{TM} survived tumor challenge. T-cell responses were also significantly higher in animals vaccinated with rV-CEA/muTRICOM^{TM}.

In CEA-Tg mice bearing CEA-positive peripancreatic tumors, 80–100% of animals died within 12 weeks without treatment. A CEA/TRICOM^{TM} vaccination regimen induced a therapeutic antitumor response as demonstrated by a 60% increase in survival through a 25-week observation period, without evidence of tumor. In CEA-Tg/MIN mice that express human CEA as a result of a transgenic insertion and develop numerous intestinal neoplasms due to a mutation in the adenomatosis polyposis coli (APC) gene, there was a spontaneous onset of intestinal tumorigenesis with strong CEA expression in all tumor cells as well as in normal gastrointestinal tissues. Vaccination with rV-CEA/TRICOM^{TM} and GM-CSF, followed by rF-CEA/TRICOMTM and rF-GM-CSF, resulted in a reduction in the number of intestinal tumors, improved overall survival (OS), and no histologic evidence of autoimmune-related pathology directed against normal tissues expressing CEA.

In clinical trials TBC-PAN-002 and CTEP No. 8087, the development of a CEA-specific T cell response was observed following treatment with PANVAC. As demonstrated in

clinical trial TBC-PAN-002, this response could be detected 2 to 6 weeks after initial treatment, and although variable, generally increased with repeated boosting immunizations.

Though TBC-PAN-003 did not meet the primary endpoint of overall survival (OS), cancer immunotherapies such as PANVAC require time for an effective immune response to develop before a clinical response can be observed (approximately 4-6 months). For example, the randomized Phase 2 trial of the poxvirus immunotherapy PROSTVAC® in metastatic castration-resistant prostate cancer (mCRPC), which resulted in a significant difference in OS (25.1 months vs. 16.6 months; hazard ratio [HR] = 0.56; p = 0.0061), did not demonstrate a significant difference in progression-free survival (PFS) (3.8 months vs 3.7 months) [88]. Similarly, the Phase 3 trial of the therapeutic cancer vaccine sipuleucel-T demonstrated a significant improvement in OS when there was not a significant difference in the shorter term endpoint of PFS [89,90]. At the time this Phase 3 trial was conducted, the median time to progression in patients with advanced metastatic pancreatic cancer who failed gemcitabine therapy was less than 10 weeks. Therefore, the clinical course of pancreatic cancer is too rapid for the clinical benefits of immunotherapy to be seen in this trial, and it was unlikely that PANVAC would improve survival as a single-agent in this patient population.

Supporting this hypothesis, in subjects with unresectable adenocarcinoma of the pancreas (clinical trial TBC-PAN-002), the median OS was 6.3 months, which is notably higher than the median OS observed in clinical trial TBC-PAN-003. Furthermore, in subjects with histologically confirmed hepatic or pulmonary metastases secondary to adenocarcinoma of the colon and rectum (clinical trial CTEP No. 8087) the median OS was significantly longer in subjects who received PANVAC compared with the contemporary control group (> 75 months in both PANVAC arms and 44.1 months in the contemporary control group; $p < 0.0001$). Additionally, some subjects with metastatic colorectal, non-colorectal, breast, or ovarian cancer (clinical trial CTEP No. 6536) had a positive clinical response to PANVAC treatment, with a number of subjects experiencing prolonged survival after coming off trial. In subjects with metastatic breast cancer (clinical trial CTEP No. 6977), PFS was higher in the PANVAC plus docetaxel arm compared with the docetaxel alone arm (7.9 months and 3.9 months, respectively [p = 0.09]). These results demonstrate the potential clinical benefit of PANVAC treatment in a variety of metastatic carcinomas.

1.10.3.2.3. Clinical Experience with CV301

CV301-2015-201

To date, CV301 has been evaluated in 12 subjects in the phase I part of the CV301-2015-201 trial sponsored by Bavarian Nordic. Clinical 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. The safety data originating from the phase I part of trial CV301-2015-201, with 12 subjects enrolled and treated, suggests that CV301 is safe and well tolerated, showing a similar safety profile as compared to the previous experience with MVA-BN-based and FPV-based vaccines.

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, 4×10^8 Inf.U, 3 have received the second dose level, 8×10^8 Inf.U, and 6 have received the highest dose level, 1.6×10^9 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 1×10^9 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 the most frequently occurring treatment-related AEs were temporary and self-limiting, grade 1 or 2 in severity and included injection site reactions (injection site erythema, pruritus, pain, induration and swelling) and general symptoms including fever/chills, flu-like symptoms, headache, fatigue/weakness, nausea/vomiting, myalgia and arthralgia.. 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. Based on this initial safety information, the trial has moved into the phase Ib part, which includes combination treatment of CV301 and nivolumab or pembrolizumab. The selected dose level for the further course of the trial was 1.6×10^9 Inf.U (i.e. 4 injections of 4×10^8 Inf.U/0.5 mL) of MVA-BN-CV301.

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

During Phase 1b, preliminary data showed that the local injection site reactions and general symptoms were in line with the experience during monotherapy in Phase 1. In total, 12 SAEs in five patients were reported. Five SAEs in two patients and four non-serious AEs in two patients led to permanent treatment discontinuation. In both Phase 1b cohorts (CV301 plus nivolumab and CV301 plus pembrolizumab), safety of the combination regimen was established. Overall, DLT and IMAE were below the pre-specified threshold to continue the trial based on the known safety profile of PD-1 inhibition. In conclusion, there appears to be no increased toxicity of the combination regimens CV301 plus pembrolizumab or nivolumab as compared to Immune Checkpoint Inhibitors alone (per Immune Checkpoint Inhibitors prescribing information).

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.

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). 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.

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. As of December 31st, 2018, seven patients were dosed with CV301 in combination with atezolizumab). Data is still preliminary.

18-C-0005 / BN-IST-013
This is an ongoing, NCI-sponsored Phase 2, single center, open lable, single-arm trial of CV301 and PROSTVAC in combination with PD-1/L1 blockade in patients with confirmed adenocarcinoma of the prostate and with a PSA over 0.8 ng/mL (following radical prostatectomy) or rise in PSA of ≥ 2 ng/mL above the nadir (definitive following radiation therapy). As of December 31st, 2018, six patients were dosed with the IMPs. Data is still preliminary.

HCRN GI16-288 / BN-IST-016
This is an ongoing, Investigator-sponsored Phase 2, multicenter, open label, randomized, two-arm trial with PD-1/L1 blockade in patients with hepatic-limited metastatic colorectal cancer foreseen for perioperative chemotherapy and surgical resection. As of December 31st, 2018, two patients were enrolled, and one patient dosed with CV301. Data is still preliminary.

1.10.4. Durvalumab Background (From the Durvalumab IB, v10.0) [2]

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.10.4.1. Summary of Non-clinical Experience

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that durvalumab inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of durvalumab. Following intravenous (IV) administration, the PK of durvalumab in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life ($t_{1/2}$) increased with increasing doses, suggesting saturable target binding-mediated clearance of durvalumab. No apparent gender differences in PK profiles were observed for durvalumab. In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study,

and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA: Durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab. Finally, data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.10.4.2. Summary of Clinical Experience

As of the data cut-off date of 12 July 2016 [2], more than 6,900 subjects have been exposed to one or more doses of durvalumab either as monotherapy, or in combination. This includes 808 patients who received durvalumab in combination with tremelimumab, and 140 who received durvalumab in combination with other investigational anticancer agents, and 186 who received durvalumab in combination with other FDA approved anticancer agents. No studies have been completed or terminated prematurely due to toxicity.

1.11.4.2.1 Pharmacokinetics and Product Metabolism

As of 24 July 2016, PK data were available for 977 patients in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W), 15 mg/kg every 3 weeks (Q3W), or 20 mg/kg every 4 weeks (Q4W). The maximum observed concentration (Cmax) increased in an approximately dose-proportional manner over the dose range of 0.1 to 20 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses <3 mg/kg and approaches linearity at doses ≥3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD L1] and membrane bound) is expected with durvalumab ≥3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, >90% of subjects are expected to maintain PK exposure ≥40 µg/mL throughout the dosing interval. As of 24 July 2016, a total of 790 subjects provided samples for ADA analysis. Overall, 25 of 790 patients (3.2%) tested positive for treatment emergent ADAs in the ADA evaluable population; 19 (2.4%) patients were persistently positive for the presence of ADA. Three patients (0.4%, in 3/790 patients) were neutralising ADA (nAb) positive. Based on population PK covariate analysis, ADA positive status was not associated with a clinically relevant reduction of exposure to durvalumab. There was no apparent effect of immunogenicity on the PK profile. At the 10 mg/kg Q2W dose, sPD-L1 suppression in ADA positive patients was similar to that observed in ADA negative patients.

1.11.4.2.2 Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis and diarrhea, pancreatitis, pneumonitis/interstitial lung disease (ILD), hepatic adverse events such as hepatitis and liver enzyme elevations, neurotoxicities such as myasthenia gravis and Guillain-Barre syndrome., endocrinopathies such as hypo- and hyper-thyroidism, hyophysitis, adrenal insufficiency and type I diabetes mellitus, dermatitis/rash, and renal adverse events such as nephritis and increase in creatinine. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below. Safety data have been pooled for 4 durvalumab monotherapy studies (CD-ON-MEDI4736-1108, D4190C00002, ATLANTIC and D4193C00001 [HAWK]) for patients who received a durvalumab dose of 10 mg/kg Q2W; a total of 1645 patients are included in this pooled data set.

- AEs reported in ≥10% of patients were fatigue (31.1%), decreased appetite (22.5%), nausea (20.5%), dyspnea (17.9%), constipation (17.8%), cough (17.4%), diarrhea (16.0%), anemia (15.3%), pyrexia (15.0%), vomiting (13.4%), back pain (12.5%), pruritus (11.0%), arthralgia (10.6%) and abdominal pain (10.2%).
- AEs that were considered by the investigator as related to durvalumab in ≥5% of patients were fatigue (14.5%); nausea (7.3%); diarrhea (6.9%); hypothyroidism (6.6%); pruritus (6.4%); decreased appetite (6.0%) and rash (5.2%).
- A total of 820 patients (49.8%) reported Grade 3 or higher AEs: of these, 487 patients (29.6%) had events of Grade 3, 63 patients (3.8%) had events of Grade 4 and 270 patients (16.4%) had Grade 5 (fatal) events. AEs of Grade 3 or higher considered related to durvalumab were reported in 164 patients (10.0%): of these, 144 patients (8.8%) had events of Grade 3, 12 patients (0.7%) had events of Grade 4 and 8 patients (0.5%) had Grade 5 (fatal) events.
- Grade 3 events occurring in ≥1% of patients were: anemia (5.5%); dyspnea (4.4%); hyponatremia (4.1%); fatigue (2.9%); GGT increased (2.7%); abdominal pain (2.0%); decreased appetite and back pain (1.9% each); pneumonia (1.8%); AST increased, and dehydration (1.6% each); hypertension (1.3%); alkaline phosphatase increased, hypokalaemia, urinary tract infection and vomiting (1.2% each); ALT increased and pleural effusion (1.1% each); bilirubin increased, asthenia, nausea and pulmonary embolism (1.0% each). Grade 3 events considered related to durvalumab occurring in ≥0.5% patients were fatigue (1.2%), GGT increased (0.8%) and AST increased (0.6%).
- The most commonly reported Grade 4 event was sepsis (0.9%), GGT increased (0.5%), dyspnea, hypercalcemia and respiratory failure (0.4%), and pneumonia (0.3%). All other Grade 4 events were reported in less than 5 patients each. Grade 4 events considered related to durvalumab occurring in ≥2 patients were GGT increased and pneumonitis (0.1% each).
- Grade 5 events occurred in the system organ class (SOC) of ‘neoplasms benign, malignant and unspecified (including cysts and polyps), with the most common Grade 5 events being general physical health deterioration (12 patients), respiratory failure (8 patients); Grade 5 events of pneumonia and sepsis occurred in 5 patients each with the remainder of the Grade 5 events occurring in ≤4 patients for each event. The only Grade 5 event considered related to durvalumab occurring in ≥2 patients was pneumonitis (0.1%).

- A total of 134 patients (8.1%) discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation were: general physical health deterioration (10 patients); pneumonitis (7 patients); pneumonia (6 patients); dyspnea and NSCLC (5 patients each); all other discontinuation events occurred in ≤4 patients.
- A total of 89 patients (5.4%) had serious treatment-emergent AEs (TEAEs) that were considered by the investigator as related to durvalumab. The most common were: pneumonitis (0.7%); fatigue (0.3%); colitis, infusion related reaction and ILD (0.2% each); dehydration, diarrhea, nausea and nervous system disorder (0.2% each); abdominal pain, acute kidney injury, adrenal insufficiency, AST increased, bilirubin increased, dyspnea, hepatic function abnormal, nephritis, transaminases increased, tumor haemorrhage and vomiting (0.1% each).
- A total of 854 patients (51.9%) experienced an AESI during the study. The most common grouped term AESI was diarrhea (16.0%, of whom 0.7% had events of Grade ≥3). Other common AESIs were: selected hepatic events (15.1%, of whom 6.9% had events of Grade ≥3); dermatitis (14.4%, of whom 0.2% had events of Grade ≥3); rash (12.1%, of whom 0.4% had events of Grade ≥3); hypothyroidism (10.3%, of whom 0.1% had events of Grade ≥3); hyperthyroidism (5.7%, of whom <0.1% had events of Grade ≥3); and select renal events (5.3%, of whom 1.0% had events of Grade ≥3). There were 6 patients who had AESIs of CTCAE Grade 5 (fatal events): three patients had hepatic events (autoimmune hepatitis; hepatic failure and hyperbilirubinemia); two patients had pneumonitis and 1 patient had immune thrombocytopenic purpura.

1.11.4.2.4 Efficacy

Efficacy data are available for three monotherapy studies (Advanced solid tumors; Myelodysplastic syndrome (MDS); and Non-small cell lung cancer (NSCLC)), and two combination therapy studies (durvalumab + dabrafenib ± trametinib in melanoma; and durvalumab + tremelimumab in NSCLC). Clinical activity has been observed across 5 studies.

Study CD-ON-MEDI4736-1108:

Patients with tumours defined as PD-L1 high (defined as tumor tissue samples that had ≥25% of tumor cells (TC) with membrane staining for PD-L1 (TC≥25%); low/negative (defined as TC<25%). In 304 NSCLC patients, the ORR, was 25% and 6% in patients with PD-L1 high and low/negative tumors, respectively and 18% in the overall population regardless of PD-L1 expression. The 12-month OS rate was 71% and 44% in patients with PD-L1 high and low/negative tumors, respectively (1st line). In 62 patients with squamous cell carcinoma of the head and neck (SCCHN), ORR was 11% across all patients, 18% in patients with PD-L1 high tumors and 8% in PD-L1 low/negative tumors. In the 61 patients with urothelial carcinoma, the ORR was 46% in the PD-L1+ subgroup compared to 0% in the PD-L1– subgroup. For other indications: In PD-L1 unselected patients, the ORR ranged from 0% in uveal melanoma to 17.4% in advanced cutaneous melanoma.

Study D4190C00007:

40 patients with MDS treated with durvalumab as a single agent in Study D4190C00007, the best overall responses were marrow complete remission (mCR) in 13 patients (32.5%); stable disease (SD) in 6 patients (15.0%); and progressive disease (PD) in 12 patients (30.0%).

ATLANTIC (NSCLC monotherapy):

In patients with locally advanced or metastatic NSCLC who had received at least 2 prior systemic treatment regimens, in the PD-L1 unselected patients (regardless of

PD-L1 TC expression) in the epidermal growth factor receptor (EGFR) wild type/unknown Cohort 2, the ORR was 10.4% (95% confidence interval [CI]: 6.2, 16.2). The response rate was similar between the non-squamous patients and the full population with the same PD-L1 expression cut off. The median OS was highest in the PD-L1 high (TC ≥25%) patients with the OS rate at 6 and 12 months of 67.4% and 47.7%, respectively. For the PD-L1 unselected patients, the OS rate at 6 and 12 months was 58.4% and 37.9%, respectively. For the patients with PD-L1 low/negative tumours, the OS rate at 6 and 12 months was 60.3% and 34.5%, respectively.

Durvalumab + BRAFi/MEKi (Study CD-ON-MEDI4736-1161):
Of the 68 patients with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 65 patients were evaluable for response. The ORR was 54.4%. The disease control rate (DCR; CR + PR + SD ≥12 weeks) was 73.5%.

Durvalumab + tremelimumab (Study D4190C00006):
Among the 75 patients with non-squamous EGFR/ALK wild type, or unknown, NSCLC, the ORR was 24.0% (18/75); for patients with PD-L1 high NSCLC it was 35.0% (7/20) and for patients with PD-L1 low/negative NSCLC ORR was 22.0% (9/14).

1.10.4.3. Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others [82-85]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [83]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [82].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommend only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

1.10.5. Individual Drug Associated Toxicities

1.10.5.1. Capecitabine [80]

Very Common (more than 1 in 10 patients)

- Fatigue

- Insomnia
- Fever
- Headache
- Diarrhea
- Hand-foot syndrome
- Stomatitis

Less Common (less than 5 in 100 patients)

- Increased liver enzymes
- Anemia
- Dehydration
- Abdominal pain
- Decrease in appetite
- Darkening of the fingers and toes
- Myelosuppression
- Acute kidney injury

Rare but serious toxicities

- Coronary vasospasm

1.10.5.2. Bevacizumab [81]

Very Common (more than 1 in 10 patients)

- Surgery and Wound Healing Complications
- Hypertension

Less Common (less than 5 in 100 patients)

- Gastrointestinal Perforations and Fistulae
- Non-Gastrointestinal Fistulae
- Hemorrhage
- Arterial Thromboembolic Events
- Venous Thromboembolic Events
- Proteinuria
- Worsening thrombocytopenia

Rare but serious toxicities

- Posterior Reversible Encephalopathy Syndrome (PRES)
- Infusion Reactions

1.10.5.3. PANVAC (As a surrogate to CV301) [1]

Very Common (more than 1 in 10 patients)

- Injection site reaction
- Fatigue
- Fever
- Flu like symptoms

Rare but Serious toxicities

- Pericardial effusion
- Abdominal pain
- Colitis
- Diarrhea
- Pancreatitis
- Alanine aminotransferase increased
- Lipase increased
- Lymphocyte count decreased
- Neutrophil count decreased
- Serum amylase increased
- White blood cell decreased

- Syncope
- Dyspnea
- Pleural effusion
- Thromboembolic events

1.10.5.4. Durvalumab [2]

Very Common (more than 1 in 10 patients)

- Diarrhea
- Fatigue
- Nausea and vomiting
- Dyspnea
- Decreased appetite
- Constipation
- Cough
- Pyrexia
- Pain in muscles and joints
- Dermatitis/Rash
- Hepatitis/Increased liver enzymes
- Anemia
- Pruritus

Less Common (>1 but <10 in 100 patients)

- Pneumonitis
- General physical health deterioration (asthenia)
- Dehydration
- Abdominal pain
- Hypertension
- Endocrinopathies including hypo- or hyperthyroidism
- Hyponatremia
- Hypokalemia
- Nephritis
- Neurotoxicities
- Infusion-related reactions
- Colitis

Rare but serious toxicities (<1 in 100 patients)

- Pancreatitis
- Type I Diabetes
- Allergic reactions
- Adrenal insufficiency
- Hypopituitarism

1.11. Hypothesis

As CV301 is capable of inducing a tumor-specific T-cell response against antigens significantly expressed in colorectal and pancreatic adenocarcinomas, and immune checkpoint inhibition can enhance the anti-tumor effect, it is hypothesized that durvalumab and CV301 will act synergistically to improve the progression-free survival rate (at 8.5 months for colorectal cancer, and 4 months for pancreatic cancer) when combined with maintenance chemotherapy from a historical 50% to a hypothesized rate of 75% or higher.

Correlative Science Hypotheses

Additionally, it is hypothesized that serial biopsies of tumor specimens will reveal the predictive value of the expression of the immune-inhibitory proteins, including PD-1, PD-L1 (B7H1), B7H3, B7H4, IDO, and arginase, and demonstrate a robust anti-tumor T-cell response in patients for whom the combination is active.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Colorectal Cancer (CRC) Arm

To determine the 8.5 month progression free survival rate ($PFS_{8.5mos}$) of durvalumab plus CV301 in combination with maintenance capecitabine and bevacizumab in patients with metastatic colorectal cancer, whose disease is stable on, or responding to 1st line therapy for metastatic disease

Pancreatic Cancer Arm

To determine the progression free survival rate (PFS_{4mos}) of durvalumab plus CV301 in combination with maintenance capecitabine in patients with metastatic pancreatic cancer, whose disease is stable on, or responding to 1st line therapy for metastatic disease

2.2. Secondary Clinical Objectives (Both Arms)

To determine, in patients treated with durvalumab plus CV301 whose disease is stable on, or responding to 1st line therapy for metastatic colorectal or pancreatic cancer:

a. Objective response rate (ORR) and duration of response
b. Progression free survival (PFS)
c. Overall survival (OS)
d. Disease control rate (DCR) (defined as ORR + rate of stable disease at 4 months)
e. Tolerability and safety of the combination

2.3. Secondary Scientific Objectives (Both Arms)

1) To assess the predictive value of immune-inhibitory proteins, including PD-1, PD-L1 (B7H1), B7H3, B7H4, IDO, and arginase; and to assess the characteristics of the infiltrating T-cells in tumor samples.
2) Using a flow-based assay, to determine the number of immune cell subsets from peripheral blood mononuclear cell (PBMC) at baseline and during treatment and attempt to identify a pattern correlating with clinical benefit.
3) To evaluate the antigen-specific T-cell activation against the target antigens of the vaccine, MUC-1 and CEA as well as other potential cascade antigens, including but not limited to brachyury.
4) To evaluate serum soluble factors and serum cytokine expression profiles at baseline and on treatment and determine correlates of clinical benefit.
5) To evaluate the relationship between tumor mutation burden and clinical benefit.
6) To evaluate the expansion of peripheral and, potentially, intratumoral T cell clones as correlates and identify correlation with clinical benefit.

2.4. Exploratory Scientific Objectives (Both Arms)

1) To assess, in patient tumor samples, the predictive value, and the changes in response to treatment of immune-inhibitory proteins and other cell signaling pathways as measured by reverse phase phosphoprotein pathway analysis of the laser capture microdissected tumor epithelium and tumor stroma/immune cell compartments.
2) To develop *ex vivo* models of patient tumors derived from patient tumor samples.

3. SUBJECT POPULATION (See Appendix A for Eligibility Checklist)

3.1. Subject population, Number of Subjects and Feasibility

3.1.1. Subject Population

Patients with metastatic pancreatic adenocarcinoma or metastatic colorectal carcinoma who are being treated with front line therapy and whose disease is stable or responding radiographically, per RECIST 1.1

3.1.2. Number of Subjects

Minimum: 28 Maximum: 52

It is estimated that a total of 46 efficacy evaluable patients will be enrolled in the study (up to 52 accounting for a drop-out rate of 10%). Specifically, a minimum of 28 patients could be enrolled in the first Simon Minimax Stage of the two Phase II portions (14 in each cohort). Each Phase II cohort will enroll a maximum of 23 evaluable patients, and allowing for a 10% dropout rate, up to 26 patients may be enrolled. Thus, the absolute minimum number of patients for the trial is 28 and the absolute maximum number of patients for the trial is 52.

3.1.3. Feasibility

Across our centers, more than 400 new cases of pancreatic cancer and 800 cases of colorectal cancer are seen yearly, at least half of whom have metastatic disease. Since at least 50% of patients with metastatic colon cancer and pancreatic cancer achieve stable disease on first line therapy, we anticipate that across our centers, at least 100 patients per year will be eligible for this trial. Nevertheless, given the barriers for recruiting any patient to a clinical trial, we conservatively estimate that recruitment will take 24 – 30 months. With each patient followed for a minimum of 8 weeks, the anticipated time to complete follow-up of all patients will be 30 – 36 months.

3.2. Inclusion Criteria

Patients must meet all of the inclusion criteria listed below in order to participate in this study:

1) Histologically proven metastatic pancreatic or colorectal adenocarcinoma with measurable disease, defined as at least 1 unidimensionally measurable lesion on a CT scan as defined by RECIST 1.1 criteria.
2) Stable on, or responding to 1st line therapy for metastatic disease
   a. Radiographically (RECIST 1.1) confirmed stable or responding disease for at least 8, and not more than 16 weeks from the initiation of 1st line therapy for metastatic disease
   b. Due to the timing of enrollment, patients who have completed a maximum of 16 weeks of 1st line chemotherapy may be enrolled >16 weeks after initiation of 1st line therapy if disease stability/response (without additional intervening therapy) can be documented within 4 weeks prior to first dose of CV301
3) Prior adjuvant chemotherapy is allowed, as long as a minimum of 3 months (for pancreatic cancer) and 6 months (for colorectal cancer) has passed between the completion of adjuvant therapy and the start of first line therapy
4) Disease that is amenable to serial biopsies
5) ECOG performance status 0-1
6) Age >= 18 years
7) Blood pressure <160/100 mmHg

8) Adequate hepatic, bone marrow, and renal function:

   a. Bone Marrow: Absolute neutrophil count (ANC) ≥ 1,500/mm^3; Platelets ≥ 100,000/mm^3; Hemoglobin ≥ 9.0 g/dL

   b. Renal function: Serum creatinine ≤ 1.5 X upper normal limit of institution's normal range OR creatinine clearance ≥ 40 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal. Creatinine clearance should be determined by the Cockcroft-Gault formula (below) or by 24-hour urine collection for determination of creatinine clearance:

   Males:

   $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

   Females:

   $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

   c. Hepatic function: AST and ALT ≤ 2.5 X the upper normal limit of institution's normal range. Non-fasting bilirubin ≤ 1.5 X the upper normal limit of institution's normal range.

9) Partial Thromboplastin Time (PTT) must be ≤ 1.5 X upper normal limit of institution's normal range and INR (International Normalized Ratio) ≤ 1.5. Subjects on anticoagulant (such as coumadin) will be permitted to enroll as long as the INR is in the acceptable therapeutic range as determined by the investigator. Due to the drug-drug interaction between warfarin and capecitabine, alternate anticoagulation should be considered.

10) Life expectancy > 12 weeks.

11) Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to initiation of treatment AND confirmed prior to initiation of treatment on Day 1.

12) Alternatively, female subjects must be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy).

13) Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consents, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

3.3. Exclusion Criteria

Any Patient who meets any of the exclusion criteria listed below at baseline will be excluded from study participation:

1) Any prior immunotherapy or vaccine therapy

2) History of active or prior documented autoimmune disease within the past 2 years including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, auto-immune Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis, with the following caveats:

   - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
   - Patients with Grave's disease, vitiligo, autoimmune alopecia, or psoriasis not requiring systemic treatment (within the past 2 years) are eligible upon consultation with the Study Chairs
   - Patients with questionable diagnosis of autoimmune disease who have never been treated with immunosuppressive regimen and have no ongoing symptoms at the time of enrollment may be eligible after discussion with medical monitor and principal investigator

3) Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and TNFα antagonists) within 28 days prior to Week 1, Day 1
    - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Study Co-chairs.
    - The use of inhaled, intranasal, ophthalmic or topical corticosteroids is allowed
    - The use of mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension is allowed.
    - Physiologic doses of systemic corticosteroids at doses which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid
    - High dose steroid pre-treatment for CT contrast dye allergy is allowed, provided the dose(s) of steroids is(are) given at least 1 week prior to starting the study medications
4) History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
5) Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
6) Positive test for HIV infection
7) Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)
    - Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive IgG antibody to hepatitis B core antigen [anti-HBc] OR negative HBV viral load by PCR) are eligible.
8) Active hepatitis C
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.
9) Active tuberculosis OR known history of previous clinical diagnosis of tuberculosis
10) Severe infections within 4 weeks prior to Week 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
11) Signs or symptoms of infection within 2 weeks prior to Week 1, Day 1
12) Received oral or IV antibiotics within 2 weeks prior to Week 1, Day 1
    - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
13) Prior allogeneic bone marrow transplantation or prior solid organ transplantation
14) Administration of a live, attenuated vaccine within 30 days before Week 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study
    - Influenza vaccination should be given during influenza season only. Patients must not receive live, attenuated influenza vaccine (e.g., FluMist™) within 4 weeks prior to Week 1, Day 1 or at any time during the study.
15) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
16) Any anti-cancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 2 weeks prior to initiation of study treatment, with the following exceptions:

- Hormone-replacement therapy or oral contraceptives
- Herbal therapy intended as anti-cancer therapy must be discontinued at least 1 week before Week 1, Day 1

17) CNS metastases including a history of leptomeningeal carcinomatosis
18) Subjects with uncontrolled seizures
19) The subject has had another active malignancy within the past five years except for cervical cancer *in situ*, *in situ* carcinoma of the bladder or non-melanoma carcinoma of the skin. Questions regarding the inclusion of individual subjects should be directed to the Principal Investigator.
20) Cardiovascular disease including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months
21) Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction
22) Life-threatening visceral disease or other severe concurrent disease
23) Grade ≥2 proteinuria at screening (or known prior)
24) Women who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not employing two highly effective and acceptable forms of contraception throughout their participation in the study and for 90 days after last dose of study drug.
25) Patients concurrently receiving any other investigational agents.
26) History of allergic reactions attributed to compounds of similar chemical or biologic composition to durvalumab or any excipient or any egg products
27) Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.4. Prior and Concomitant Therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at Screening up to the Final Visit must be recorded in source documents and the case report forms (CRFs). The reason for use, date(s) of administration (including start and end dates), and dosage information (including dose and frequency) must be recorded. Any change in concomitant therapy during the study period must be similarly recorded. Questions regarding prior or concomitant therapy should be directed to one of the investigators.

3.4.1. Prior Anticancer Therapy

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (cytotoxic chemotherapy, immunotherapy, or biologic therapy), radiotherapy, and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans.

3.4.2. Prior Surgery

Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies, tumor biopsies, or mediport placement may only require a 24 hour waiting period, but this must be discussed with an investigator.

3.4.3. Supportive Care

Subjects should receive best supportive care and treatment of symptoms during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support,

intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.). Medications, including steroids, which are given for supportive care, such as appetite stimulation, may be given concurrently. Management of immune-related complications, including the use of steroids, is detailed below in Section 5.10.

3.4.4 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 3.4.5.

3.4.5 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapies
2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. ***NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).***
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, intranasal, ophthalmic and topical corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
4. Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Rescue/supportive medication/class of drug	Usage
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.])	Should be used when necessary for all patients

Table 1. Prohibited and Rescue Medications

3.5. Removal/replacement of Subjects from Therapy or Assessment

The study requires that 46 efficacy evaluable subjects be enrolled. An efficacy evaluable patient must meet all inclusion/exclusion criteria, and be evaluable for the primary endpoint of $PFS_{8.5mos}$ (colorectal cancer) or PFS_{4mos} (pancreatic cancer)

3.5.1. Screen Failures

Patients will be identified and enrolled while still receiving first-line therapy. All patients must continue to meet the inclusion and exclusion criteria up to and including the first day of treatment on the study

medications. Reasons for patients who have enrolled, but become ineligible could include (but are not limited to):

- The patient is no longer eligible based on laboratory parameters
- The patient's performance status has declined
- The patient no longer has measurable disease

Patients who become ineligible during the course of first-line therapy, prior to initiation of study medications will be considered screen failures. Screen failures must be replaced until a maximum of 46 evaluable patients are enrolled or study termination, whichever occurs first.

3.5.2. Evaluable Patients

3.5.2.1 Evaluable for Toxicity

Patients must complete 4 weeks of therapy – enough to have received at least one dose of CV301 and durvalumab to be assessable for toxicity. Patients who are taken off study prior to receiving the first dose of durvalumab will need to be replaced.

3.5.2.2. Evaluable for Efficacy

Of note, any patient who initiates study medications, and is taken off study prior to 8.5 months (colorectal cancer) or 4 months (pancreatic cancer) for disease progression or clinical progression, including death related to the underlying pancreatic or colorectal cancer (as determined by the treating oncologist) will be considered efficacy evaluable. However, patients who have initiated study medications, and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed related to their underlying pancreatic or colorectal cancer will not be considered evaluable for efficacy. These patients will need to be replaced for the efficacy analysis. Reasons for patients who have initiated study medications, but are no longer evaluable could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping second-line therapy
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying pancreatic or colorectal cancer
- An unexpected trauma or death that is considered unrelated to the underlying pancreatic or colorectal cancer

3.6. Multi-institutional Trial Coordination

See Appendix B for the patient registration form

3.6.1. Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator and a data manager

In addition, Georgetown University's Multicenter Project Management Office will oversee the conduct of the trial Lombardi-Georgetown and additional sites. Georgetown University's Multicenter Project Management Office will be the main point of contact for the study chair, Dr. Pishvaian and the other site PIs for any study related concerns, including data management and regulatory.

3.6.2. Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's screening number and initials, to the site PI, Dr. Pishvaian, and to Georgetown University's Multicenter Project Management Office. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's Quality Assurance Office (QAO) by secure email or fax to confirm eligibility. Patients should not start therapy until Dr. Pishvaian and Georgetown

University's QAO have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

3.6.3. Data collection and management

Patient data will be entered into the on-line accessible database (the database will be built with case report forms (CRFs) at Georgetown upon trial approval). This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to initiating any study related activities, and all ongoing patient data should be entered within one week of each patient visit.

3.6.4. Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

3.6.5. Trial Auditing

Georgetown University's Multicenter Project Management Office will provide annual trial auditing for this study. Georgetown University's Multicenter Project Management Office will arrange all primary source documents for the patients from all sites to be audited. Auditing of the study will occur at Lombardi-Georgetown, but will be performed on a random sampling of the patients selected from any site.

4. STUDY PROCEDURES

4.1. Study Overview

Basic Study Design

This is a dual arm, open label phase II study to evaluate the safety and clinical activity of the combination of durvalumab with CV301 plus maintenance chemotherapy for patients with metastatic colorectal or pancreatic cancer whose disease is stable on, or responding to 1st line therapy for metastatic disease. Patients with metastatic colorectal or pancreatic adenocarcinoma who still have an adequate performance status and normal hepatic and renal function will be eligible.

The trial will consist of two parallel Phase II trials – one for patients with metastatic colorectal cancer, and one for patients with metastatic pancreatic cancer (Figure 5). In the Phase II portion, patients will be seen every two weeks through eight weeks, and then routinely every 4 weeks thereafter for as long as the patient is on study. Adverse events will be monitored throughout the trial (safety tests will be performed every 2 weeks for the first 8 weeks, and then every 4 weeks thereafter) and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Restaging studies will be performed every 8 weeks (+/- 5 days) (typically CT scans), by the calendar. Patients whose tumors have not progressed at the time of restaging, and who continue to tolerate treatment will continue on study.

The study is estimated to last 36 months. Patient treatment will continue until disease progression, death, or until the physician or patient request removal from the study for any reason.

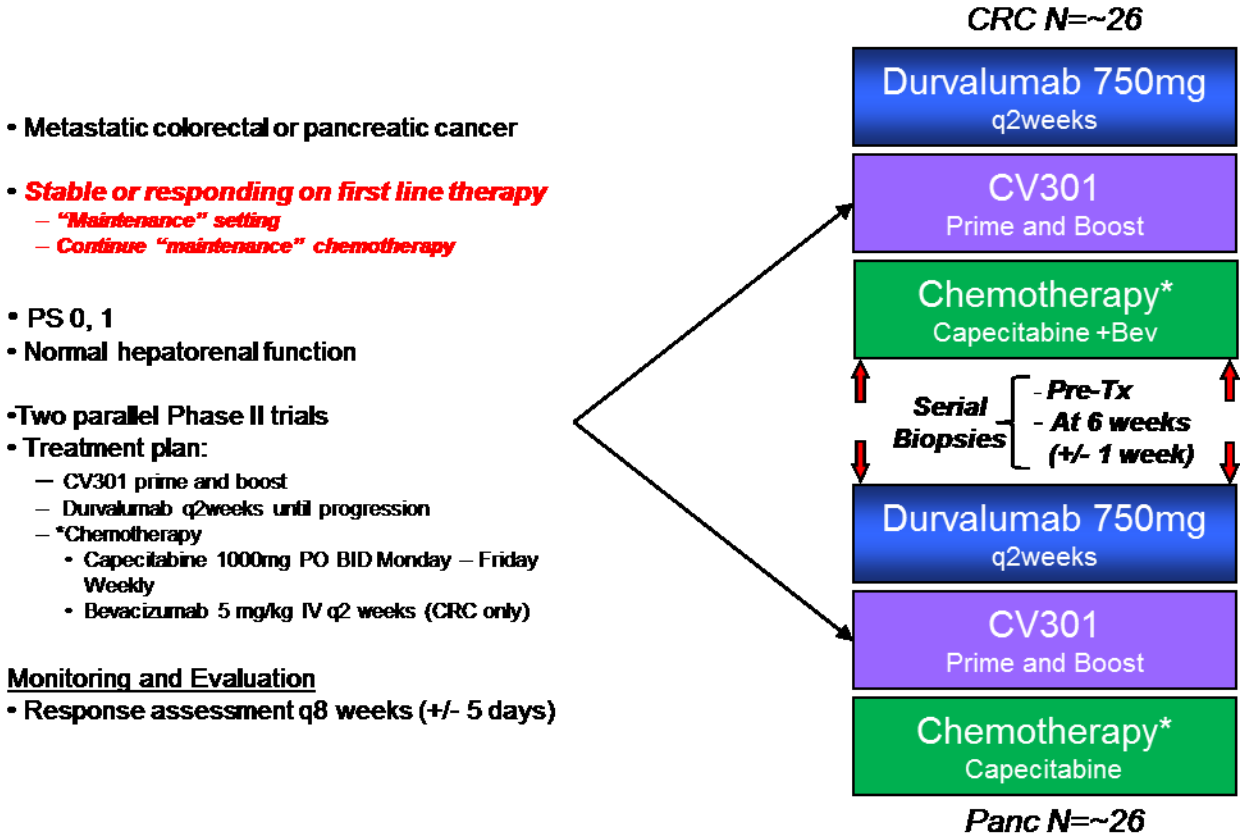


Figure 3 (Figure 1 repeated): Trial Schema

Response Assessment

The primary efficacy objective is to determine the $PFS_{8.5mos}$ in the colorectal cancer arm, and PFS_{4mos} in the pancreatic cancer arm. Disease response/progression will be assessed according to RECIST 1.1. However, RECIST 1.1 will be adapted to account for the potential of pseudoprogression, in which immune-mediated tumor infiltration may lead to an initial increase in the size of the tumors, and can lead to a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, standard RECIST 1.1 criteria may not provide an accurate response assessment of immunotherapeutic agents such as durvalumab and CV301. Therefore, RECIST 1.1 will be used with the following adaptations, as detailed in Section 6:

If radiologic imaging shows initial PD, but patients are adequately tolerating therapy, patients may continue therapy until the next restaging while awaiting radiologic confirmation of progression. The decision to continue therapy should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease:

- If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy.

Study Product, Dose, Route, Regimen

Please note that for all durvalumab and CV301 (and bevacizumab for the colorectal cancer patients), treatments and subject assessments may occur +/- 3 days to accommodate patient scheduling

Patients will begin maintenance chemotherapy beginning Week 1. This will be dosed as capecitabine 1000mg orally twice a day given Monday – Friday every week. In addition, colorectal cancer patients will receive maintenance bevacizumab, dosed at 5mg/kg IV q2weeks

The order in which the drugs will be administered is based on the fact that the durvalumab can be associated with infusion reactions – whereas the risk of infusion/administration reaction with bevacizumab and CV301 is extremely low. The drugs should be administered:

1) Capecitabine 1000mg PO BID weekly M-F will be ongoing oral administration and can be started at any time on the days of administration of the other agents
2) Durvaluamab over approximately 60 minutes (±5 minutes)
   a. Note: The first dose of durvalumab is to be given over 90 minutes (±5 minutes)
3) Bevacizumab 5mg/kg (Based on weight at screening unless 10% change) IV over 60 minutes (±5 minutes) Q2weeks
4) MVA-BN-CV301 (prime) - two priming doses of MVA-BN-CV301 given s.c. on Day 1 and Day 29. One dose of MVA-BN-CV301 consists of 4 injections of 4 X 10^8 Inf.U in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6 x 10^9 Inf.U per dose.
5) FPV-CV301 (boost) - One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1x10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh on Day 1 of Weeks 9, 13, 17, 21, 25, 37, and q24 weeks starting week 53.

To intensify the opportunity for activation of tumor-infiltrating antigen-specific CD8 killer T cells (expressing high levels of IFN-gamma), whose anti-tumor activity would be enhanced by immune checkpoint blockade, we will employ a prime-boost treatment plan. Thus, patents first receive two priming

doses with MVA-BN-CV301 given s.c. on Day 1 and Day 29. One dose of MVA-BN-CV301 consists of 4 injections of 4 X 10^8 Inf.U in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6 x 10^9 Inf.U per dose. Then, starting week 9, patients will begin therapy with FPV-CV301. One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1x10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh on Day 1 of Weeks 9, 13, 17, and 21; and then weeks 25 and 37: and then starting week 53 q24 weeks continuously until progression.

Week 3, Day 1, patients will also begin therapy with durvalumab, which will be subsequently given every two weeks until progression (or intolerance).

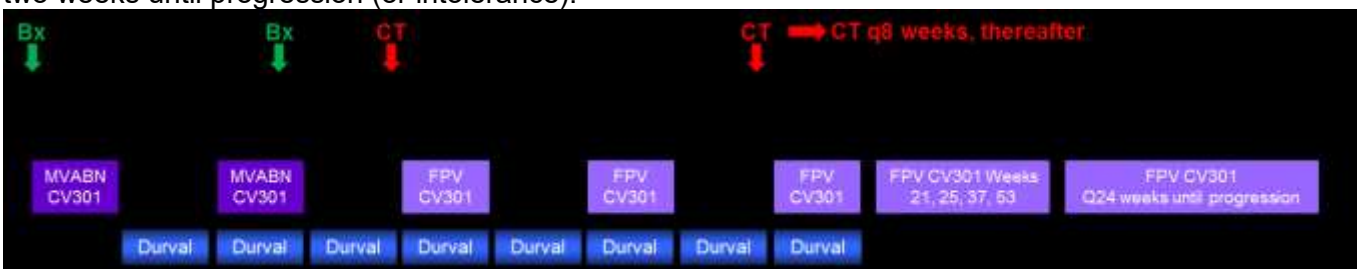


Figure 4 (Figure 2 repeated): Durvalumab plus CV301 Treatment Schedule

Durval = Durvalumab

Duration of administration

Durvalumab and FPV-CV301 will continue until disease progression (or intolerance). Maintenance chemotherapy (capecitabine (+ bevacizumab for CRC)) will also continue until disease progression (or intolerance). However, in the unlikely event of a complete response, patients may stop the maintenance chemotherapy and continue the durvalumab and FPV-CV301 alone after 52 weeks (one year). Patients who stop maintenance chemotherapy after 52 weeks, and whose disease then begins to progress/recur may be restarted on the maintenance chemotherapy until further disease progression.

4.2. Patient Screening

The screening window is 2 weeks prior to the first dose of CV301. Study activities are detailed in Table 4, and a study activity checklist in Table 5. Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. For procedures performed at screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment. If any abnormality that would be an exclusion is identified at subject assessment at any time prior to initiating therapy on Day 1, the patient will not start treatment until the abnormality is resolved, and the patient again meets all inclusion/exclusion criteria. The screening procedures include the following listed below.

4.2.1. Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken.

4.2.2. Medical History

- Complete medical and surgical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Presence and severity of any symptoms/conditions associated with colorectal or pancreatic cancer
- Detailed oncology history, including:
  - Date of primary cancer diagnosis
  - Pathology (histology or cytology) of primary tumor
  - Metastasis information (including the location)

- Surgical history (if any)
- Anti-cancer and radiation treatments administered (including dates and type of modality)

- At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded in the case report form (CRF). On Week1, Day 1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the off study visit.

4.2.3. Demographics

Age, gender, race and ethnicity will be recorded

4.2.4. Review Subject Eligibility Criteria

4.2.5. Review previous and concomitant medications

4.2.6. Physical Exam Including Vital Signs, Height, and Weight

A complete physical examination will be performed at the Screening Visit. Body weight will be recorded during every physical exam. The subject will wear lightweight clothing and no shoes during weighing. Height will be measured at the Screening Visit only; the subject will not wear shoes.

4.2.7. Vital Sign Determinations

Heart rate, blood pressure, respiratory rate, and body temperature will be obtained at the Screening Visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

4.2.8. Hematology

Hematology samples (CBC) will be collected and assessed using a certified laboratory. The Investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.2.9. Serum Chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate, magnesium), glucose, and total bilirubin. Creatinine clearance will be calculated as per section 3.2. Amylase and lipase will be collected at screening, Week 1, Day 1 and every two weeks through week 9, and then every 4 weeks thereafter. TSH will be collected at screening, and every 8 weeks starting week 9. Hepatitis and HIV serologies will be collected at screening only.

4.2.10. Urinalysis

4.2.11. Pregnancy Test and Pregnancy Prevention

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening Visit within 14 days of Week 1, Day 1 and a urine pregnancy test will be done at the Week1, Day 1 visit prior to the first dose of study drug. Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year). The test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at Week1, Day 1, it should be confirmed by a serum pregnancy test. The test may be repeated at the discretion of the investigator at any time during the study. Should a female study subject become

pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately.

Females of childbearing potential who are sexually active with a nonsterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of durvalumab or CV301; cessation of birth control after this point should be discussed with a responsible physician. While total abstinence is an acceptable method to prevent pregnancies, neither periodic abstinence (also considered the rhythm method), nor the withdrawal method are acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Subjects must use 2 acceptable methods of effective contraception as described in Table 4.
- Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 4) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Combined pill
		Minipill
		Patch

Table 2. Effective Methods of Contraception. Two methods must be used.
[a]This is also considered a hormonal method.

4.2.12. Tumor Assessment

Only patients with metastatic pancreatic or colorectal cancer not eligible for resection will be considered for entry. Subjects must have measurable disease, defined as at least 1 measurable lesion as defined by RECIST 1.1. Imaging for screening will be reviewed to prepare for tumor biopsies and to determine stable or responding disease (per RECIST 1.1) on 1st line therapy.

4.2.13. Electrocardiogram

Electrocardiograms (ECGs) obtained at screening, will be obtained in triplicate (with 2-5 minute lag time between each). Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes. QT interval corrected for heart rate should be calculated using Fridericia's formula (QTcF).

4.2.14 Performance Status

Performance status will be evaluated prior to study entry according to the table below:

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

Table 3: ECOG Performance Status

4.2.15 Adverse Event Assessment

Baseline adverse events will be assessed. See Section 7 for Adverse Event monitoring and reporting. The Investigator will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by:
Common Terminology Criteria for Adverse Events, Version 4.0, NCI, NIH, DHHS. June 14, 2010.
Available at: CTCAE version 4.03 - 2010-06-14

4.3. Patient Enrollment

A minimum of 2 weeks must have passed before any prior chemotherapy or radiation therapy received during the course of first-line therapy before patients can begin study medications (i.e. at least 14 days prior to Week 1 of therapy). The patient must meet all inclusion/exclusion criteria, including laboratory parameters, prior to study medication initiation. Any patient who does not meet inclusion/exclusion criteria may be re-evaluated once any excluding factors are mitigated. But any patient who does not ultimately meet inclusion/exclusion criteria will be considered a screen failure, and will be replaced on the study.

4.3.1. Patient Study Number Assignment and Sample Labelling

Though out the study, the following labelling procedure will be followed.

4.3.2. Patient Study Number Assignment

Patients will be de-identified and labelled with a 5 character study label (AA-X-XX):

- The first two characters will be the patient's initials
- The third character will be the site from which the patient was enrolled (single digit)
  - 1 = Georgetown
  - 2 = Mayo Clinic
  - 3 = MD Anderson
  - 4 = Emory University
- The fourth and fifth characters will be the patient study number (e.g. 01, 02, 03, etc.)

4.3.3. Sample Labelling (Appendix C)

For all correlative samples that are stored at one of the study sites, patient labels will be de-identified and labelled with a 14 character study label (AA-X-XX-XX-X-MM/DD/YY):

- The first two characters will be the patient's initials
- The third character will be the site from which the patient was enrolled (single digit)
  - 1 = Georgetown
  - 2 = Mayo Clinic
  - 3 = MD Anderson
  - 4 = Emory University
- The fourth and fifth characters will be the patient study number (e.g. 01, 02, 03, etc.)
- The sixth and seventh characters will be the correlative technique (two digit)
  - 01 = NIH Formalin
  - 02 = George Mason RPPA
  - 03 = NIH Frozen
  - 04 = TJU Organoids
  - 05 = Lombardi Zebrafish
  - 06= Blood collection: Serum and PBMC
  - Additional numbers can be added as needed for future research samples
- The eighth character will be the timing of collection
  - 1 = Pre-treatment biopsy/sample
  - 2 = On treatment biopsy/sample
  - 3 = Serum collection

- The final characters will be the date in MM/DD/YY format

Example: AA-1-01–01-1-10/14/18
Protocol: 2017-1189

4.3.4. Tumor Biopsies and Blood Collection

A rigorous tumor collection algorithm will be instituted for this protocol. Biopsy sample prioritization, as well as shipping details and addresses are all summarized below, in greater detail in Section 9, and in Appendix C.

Please note: Details on collection and shipping, particularly details on the acquisition of supplies and the personnel involved are subject to change. Thus, details on collection and shipping in the Lab Manual are to be considered the most updated (note the Version number and dates).

Of note, patients who are on chronic anticoagulation will be required to hold anticoagulation prior to the biopsies being performed. Patients on warfarin must hold treatment for 5 days, but will be on low-molecular weight heparin (LMWH), 1 mg/kg subcutaneously twice a day. The LMWH will continue until the last biopsy is complete. Patients may then resume warfarin the day after the last biopsy. Additionally, patients on LMWH will hold (i.e., not receive) the dose of LMWH the morning of the procedure, but will resume the LMWH the evening of the day of the biopsy.

4.3.4.1. Tumor Biopsy Tissue Utilization and Prioritization

For the pre-treatment and week 6 biopsy, six individual cores will be obtained with an 18-20 gauge needle. The cores will be prepared as follows (and as depicted in Appendix C):

- The first two cores (Correlative sample and phosphoprotein sample) should be placed INDIVIDUALLY in a single standard formalin vials and submitted to surgical pathology for paraffin embedding. The samples from these FFPE block **should not be cut** for an H&E analysis. Rather, the block will be requested from surgical pathology, and sent in batches to Dr. Schlom at the NIH (First core) and to George Mason University to Dr. Petricoin's lab (second core) for laser capture microdissection of tumor epithelium and stroma for Reverse Phase Protein Microarray (RPPA) analysis.

- The next two cores (Correlative samples) should be placed INDIVIDUALLY in a single cryovials and snap frozen in liquid nitrogen, and stored at -80^{o}C. These frozen samples will be shipped in batches on dry ice to Dr. Schlom at the NIH.

- The fifth core (organoid sample) will be collected for organoids will be collected in pre-supplied Eppendorf tubes containing Advanced DMEM/F12 (5mL) with Glutamax 1%, Pen/Strep 1%, and HEPES Buffer 1%. Media will be sent to the sites in batches of 10 upon request from Dr. Brody's lab. Samples will be collected, and shipped overnight on WET ice to Dr. Brody's lab.

- The sixth core will be placed in a pre-provided Eppendorf tubes with CRC media with y-compound. This will be shipped on WET ice to the Shared Resources core, c/o Dr. Byers, at the Lombardi Cancer Center.

4.3.4.2. Serial Blood Collection

On the first treatment day (Week 1, CV301 alone), and on weeks 9, 17, and 49, and at the off study visit 6 green top (Na heparin, 10 mL) tubes and 2 red serum separator (8 mL) tubes will be obtained. Shipping details are provided in Appendix C.

4.4. Detailed Patient Assessments

Study activities are detailed in Table 4, and a study activity checklist in Table 5. *Please note that for patient assessments may occur +/- 3 days to accommodate patient scheduling*

4.4.1. Subject Assessments

Patients will be seen on Week1, Day 1, then every two weeks through eight weeks, and then routinely every 4 weeks thereafter for as long as the patient is on study, and at the Final Visit.

4.4.2. Physical Examinations

A complete physical examination will be performed on Week1, Day 1, then every two weeks through eight weeks, and then routinely every 4 weeks thereafter for as long as the patient is on study, and at the Final Visit. A complete physical examination will include: weight, vital signs, performance status, hematology samples, and a comprehensive metabolic panel. Any significant physical examination findings after the administration of the first dose of the experimental therapy will be recorded as adverse events. The subject will wear lightweight clothing and no shoes during weighing.

4.4.3. Updated Medical History

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded in the CRF. On Week1, Day 1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the off study visit.

4.4.4. Vital Signs

Vital sign determinations of heart rate, blood pressure, respiratory rate, and body temperature will be obtained on Week1, Day 1, then every two weeks thereafter for as long as the patient is on study, and at the Final Visit. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. On durvalumab treatment days, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes (such as with the first infusion, which lasts 90 minutes), then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses, the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

4.4.5. Tumor Markers

Tumor markers such as a CA 19-9 and/or CEA should be checked every 4 weeks. The actual marker(s) will be at the discretion of the treating physician – but at least one marker should be checked.

4.4.6. Correlative Blood Samples

Correlative blood samples will be obtained on the first treatment day (Week 1, CV301 alone), and on weeks 9, 17, and 49, and at the off study visit.

4.4.7. Clinical Laboratory Tests

All subjects will undergo the laboratory assessments outlined in Table 4. Hematology and chemistry samples (including magnesium) will be collected at the screening visit, at Week 1 and every 2 weeks thereafter. Creatinine clearance will be calculated as per section 3.2. PT/PTT/INR will be collected at during screening, and at the visit week 6 (prior to the second biopsy). Amylase and lipase will be collected at screening, Week 1, Day 1 and every two weeks through week 9, and then every 4 weeks thereafter. TSH will be collected at screening, and every 8 weeks starting week 9. Hepatitis and HIV

serologies will be collected at screening only. Laboratory samples for this study will be assessed using the certified laboratory at the individual sites, and these data will be used for all data analysis. The Principal Investigator or sub-investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 7.

4.4.8 Electrocardiograms

Electrocardiograms (ECGs) will be obtained during screening, prior to starting durvalumab at the week 3 visit and the week 9 visit, and at the end of treatment, as well as at any other time point when clinically indicated. ECGs recorded during the screening period will be obtained in triplicate (with 2-5 minute lag time between each); ECGs recorded during the treatment phase will be single tracing. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. At the week 3 and week 9 visit, ECGs will be recorded within an hour prior to start of infusion of durvalumab and at least one time point 0 to 3 hours after the infusion. QT interval corrected for heart rate should be calculated using Fridericia's formula (QTcF).

4.4.9 Urinalysis

A urinalysis should be performed at screening, and prior to treatment at the week 9 visit, and every 8 weeks thereafter.

4.4.10 Imaging and Response Evaluation

Patients will undergo a baseline tumor evaluation with imaging studies within four weeks of Week 1, Day 1(unless disallowed by patient's insurance and/or the patient has had imaging within 4 weeks of starting therapy). Imaging studies should include a diagnostic CT scan of the chest, abdomen, and pelvis (as well as any other known sites of disease (e.g. neck)) with PO and IV contrast. Patients may undergo other modalities such as an MRI instead of a CT scan at the treating physician's discretion if appropriate (such as patient allergy to CT contrast, extremity tumors, bone metastases requiring bone scans, etc.). Response evaluation will occur at 8 weeks (+/- 5 days), and then at 16 weeks (+/- 5 days), and every 8 weeks thereafter (+/- 5 days), and at the Final Visit (+/- 5 days), if not performed within the last four weeks. Tumor response and/or disease progression will be assessed by the modality(ies) used prior to treatment. If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery. Patients will continue to remain on study as long as there is no evidence of progression of disease and the therapy is adequately tolerated.

4.4.11 Adverse Event Evaluation (See Section 5 for Full Details)

The Principal Investigator or Sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 4.0.
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf
The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

4.4.12 Final Visit and Survival Follow-up

When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted. At the Final Visit, patients will undergo a subject assessment (physical examination, vital

signs, performance status, chemistry, hematology, medication review, and adverse event evaluation). Additionally, information pertaining to survival and post treatment therapy will be collected approximately every 12 weeks (Months 3, 6, 9, 12, 15 and 18) beginning after the final visit, for a period up to 24 months. Patients will be followed by phone or mail every 3 months after completion of (or early withdrawal from) study treatment for survival analysis until death or 12 months, whichever comes first.

If a research subject cannot be located to document survival after the final visit, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented for review by the DSMC.

4.5. Removal of Subjects from Study

Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study if any of the following occur:

1) The subject experiences either clinical or radiographic progressive disease as defined in Section 6.
2) The subject experiences toxicity that makes continuation in the protocol unsafe as defined in Section 5.
3) Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study.
4) The subject requires radiotherapy or alternate antineoplastic agents during the study period.
5) The investigator believes it is in the best interest of the subject.
6) Clinically significant deterioration of the subject's medical status as determined by the investigator.
7) The subject requires alternative anti-cancer agents or non-palliative radiation therapy for primary or metastatic disease during the treatment portion of the study.
8) The subject becomes pregnant or begins breastfeeding during the treatment portion of the study.
9) The subject or subject's legally acceptable representative decides to withdraw consent for any reason.
10) The subject is unable to comply with protocol requirements.
11) Any other medical reason that the study investigator deems appropriate.

4.5.1. Discontinuation of Individual Subjects

When a subject discontinues from the study (without reaching a protocol-defined endpoint) is planned, the investigator will notify the principal investigator as soon as possible (provided, in each case, subject care and safety are not compromised). When a subject discontinues the study, a final visit will be conducted (preferably prior to the initiation of another anticancer therapy). However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the investigator's best clinical judgment. At the final visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, collection of unused study drug and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. All subjects will have one follow-up visit approximately 30 days after the final visit. This follow-up visit does not need to be performed for

subjects who have had a final visit conducted ≥ 30 days after discontinuation of study drugs. If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved. In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of study drug to that subject must be discontinued immediately.

4.5.2. Discontinuation of the Entire Study

The investigators may terminate this study provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

1) If the investigators have decided to prematurely discontinue the study, the investigators will promptly notify in writing the IRB of the decision and give detailed reasons for the discontinuation.
2) The principal investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

Table 4a: Study Activities to Week 24

	Screening (Day -14 to Day -1)	Week 1	Week 3	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	Week 13	Week 15	Week 16	Week 17	Week 19	Week 21	Week 23	Week 24	Off Study	Follow-up[p]
Informed consent	X																		
Demographics	X																		
Medical history	X																		
Concurrent meds	X	X	X	X		X		X		X			X		X			X	
β-HCG	X[a]	X[a]																	
Vital signs	X	X	X	X		X		X	X	X	X		X	X	X	X		X	
Height	X																		
Weight	X	X	X	X		X		X	X	X	X		X	X	X	X		X	
History and Physical	X	X	X	X		X		X		X			X		X			X	
Performance Status	X	X	X	X		X		X		X			X		X			X	
Adverse event evaluation	X	X	X	X		X		X		X			X		X			X	
Dispense Capecitabine[b]		X		X				X		X			X		X				
Dispense Bevacizumab[c] (Colorectal Cancer Only)		X	X	X		X		X	X	X	X		X	X	X	X			
Dispense MVA-BN-CV301		X		X															
Dispense FPV-CV301								X		X			X		X				
Dispense Durvalumab[d]			X	X		X		X	X	X	X		X	X	X	X			
CBC w/diff	X	X	X	X		X		X	X	X	X		X	X	X	X		X	
Serum chemistry[e]	X	X	X	X		X		X	X	X	X		X	X	X	X		X	
Magnesium	X	X	X	X		X		X	X	X	X		X	X	X	X		X	
Amylase and Lipase	X	X	X	X		X		X		X			X		X			X	
TSH (Reflex Free T4 and Total T3 if TSH is abnormal)	X							X					X					X	
Urinalysis	X							X					X						
Hepatits and HIV Serologies[f]	X																		
Tumor Markers[g]		X						X		X			X		X			X	
Electrocardiogram[h]	X		X					X										X	
Radiologic evaluation and Tumor Measurements[i]	X						X					X					X	X[k]	
PT/PTT[l]	X				X														
Tumor Biopsy[m]	X				X														
Research Blood Samples[p]		X						X					X					X	
Survival																			X[r]

Please note that for all durvalumab and CV301 (and bevacizumab for the colorectal cancer patients), treatments and subject assessments may occur +/- 3 days to accommodate patient scheduling

[a]For women of childbearing potential, serum pregnancy test during screening; and urine pregnancy test on Week 1, Day 1

[b]Capecitabine BID M-F every week, commercial Supply, enough for four weeks

[c]Bevacizumab, commercial Supply; - Bevacizumab should be given IV over 60 minutes for the first two infusions, and then over 30 minutes thereafter

[d]On durvalumab treatment days, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion

[e]Serum chemistries include: albumin, alkaline phos, total bili, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium

[f]Hepatitis B surface antigen (reflex HBV viral load if sAg positive); Hepatitis C antibody (Reflex HCV RNA if antibody positive); HIV test

[g]Tumor markers include CA 19-9, or CEA, as appropriate

[h]Triplicate Electrocardiograms will be performed at Screening. ECGS obtained during week 3, week 9, and EOT will be single tracing only to assess QTcF. ECGs obtained during treatment with durvalumab (Weeks 3 and 9) will be obtained within an hour prior to start of infusion of durvalumab and at least one time point 0 to 3 hours after the infusion.

[i]Screening scans should be within 4 weeks of starting treatment; Response scans must be performed every 8 weeks (+/- 5 days) to assess response

[k]Unless performed within 4 weeks of the off study date

[l]For Biopsies

[m]Pre-treatment biopsy may occur any time from consent to Day -1; On study biopsy may occur +/- 1 week of week 6

[p]Six green top (Na heparin, 10 mL) tubes, 2 red serum separator (8 mL) tubes

[r]Follow up Assessments may be through office visits, or telephone follow-up and should be approximately every 12 weeks

Table 4b: Study Activities Week 25-51

	Week 25	Week 27	Week 29	Week 31	Week 32	Week 33	Week 35	Week 37	Week 39	Week 40	Week 41	Week 43	Week 45	Week 47	Week 48	Week 49	Week 51	Off Study	Follow-up[p]
Concurrent meds	X		X			X		X			X		X			X		X	
Vital signs	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	
Weight	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	
History and Physical	X		X			X		X			X		X			X		X	
Performance Status	X		X			X		X			X		X			X		X	
Adverse event evaluation	X		X			X		X			X		X			X		X	
Dispense Capecitabine[b]	X		X			X		X			X		X			X			
Dispense Bevacizumab[c] (Colorectal Cancer Only)	X	X	X	X		X	X	X	X		X	X	X	X		X	X		
Dispense FPV-CV301	X							X											
Dispense Durvalumab[d]	X	X	X	X		X	X	X	X		X	X	X	X		X	X		
CBC w/diff	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	
Serum chemistry[e]	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	
Magnesium	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	
Amylase and Lipase	X		X			X		X			X		X			X		X	
TSH (Reflex Free T4 and Total T3 if TSH is abnormal)	X					X					X					X		X	
Urinalysis	X					X					X					X			
Tumor Markers[f]	X		X			X		X			X		X			X		X	
Electrocardiogram[g]																		X	
Radiologic evaluation and Tumor Measurements[h]					X					X					X			X[i]	
Research Blood Samples[m]																X		X	
Survival																			X[p]

Please note that for all durvalumab and CV301 (and bevacizumab for the colorectal cancer patients), treatments and subject assessments may occur +/- 3 days to accommodate patient scheduling

[b]Capecitabine BID M-F every week, commercial Supply, enough for four weeks

[c]Bevacizumab, commercial Supply; - Bevacizumab should be given IV over 60 minutes for the first two infusions, and then over 30 minutes thereafter

[d]On durvalumab treatment days, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion

[e]Serum chemistries include: albumin, alkaline phos, total bili, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium

[f]Tumor markers include CA 19-9, or CEA, as appropriate

[g]ECGS obtained at the EOT will be single tracing only to assess QTcF.

[h]Response scans must be performed every 8 weeks (+/- 5 days) to assess response

[i]Unless performed within 4 weeks of the off study date

[m]Six green top (Na heparin, 10 mL) tubes, 2 red serum separator (8 mL) tubes

[p]Follow up Assessments may be through office visits, or telephone follow-up and should be approximately every 12 weeks

Table 4c: Study Activities Week 53 on...

	Week 53	Every 2 weeks, Week 55 until progression	Every 4 weeks, Week 57 until progression	Every 8 weeks, Week 56 until progression	Every 8 weeks, Week 57 until progression	Every 24 weeks, Week 53 until progression	Off Study	Follow-up[p]
Concurrent meds	X		X				X	
Vital signs	X	X	X				X	
Weight	X	X	X				X	
History and Physical	X		X				X	
Performance Status	X		X				X	
Adverse event evaluation	X		X				X	
Dispense Capecitabine[b]	X		X					
Dispense Bevacizumab[c] (Colorectal Cancer Only)	X	X	X					
Dispense FPV-CV301	X					X		
Dispense Durvalumab[d]	X	X	X					
CBC w/diff	X	X	X				X	
Serum chemistry[e]	X	X	X				X	
Magnesium	X	X	X				X	
Amylase and Lipase	X		X				X	
TSH (Reflex Free T4 and Total T3 if TSH is abnormal)					X		X	
Urinalysis					X			
Tumor Markers[f]	X		X				X	
Electrocardiogram[g]							X	
Radiologic evaluation and Tumor Measurements[h]				X			X[i]	
Research Blood Samples[m]							X	
Survival								X[p]

Please note that for all durvalumab and CV301 (and bevacizumab for the colorectal cancer patients), treatments and subject assessments may occur +/- 3 days to accommodate patient scheduling

[b]Capecitabine BID M-F every week, commercial Supply, enough for four weeks

[c]Bevacizumab, commercial Supply; - Bevacizumab should be given IV over 60 minutes for the first two infusions, and then over 30 minutes thereafter

[d]On durvalumab treatment days, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion

[e]Serum chemistries include: albumin, alkaline phos, total bili, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium

[f]Tumor markers include CA 19-9, or CEA, as appropriate

[g]ECGS obtained at the EOT will be single tracing only to assess QTcF.

[h]Response scans must be performed every 8 weeks (+/- 5 days) to assess response

[i]Unless performed within 4 weeks of the off study date

[m]Six green top (Na heparin, 10 mL) tubes, 2 red serum separator (8 mL) tubes

[p]Follow up Assessments may be through office visits, or telephone follow-up and should be approximately every 12 weeks

Table 5: Study Activities Checklist (With Specific Details Through Week 16)

Screening (Within 2 weeks of Cycle 1, Day 1)

Subject Assessment	_____
Eligibility Criteria	_____
Informed Consent	_____
Pregnancy Test (if appropriate)	_____
Radiology Evaluation and Tumor Measurements	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Height and Weight	_____
Vital Signs	_____
Performance Status	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Amylase and Lipase	_____
TSH (Reflex Free T4 and Total T3 if TSH abnormal)	_____
Urinalysis	_____
Hepatits and HIV Serologies	_____
PT/INR, PTT	_____
Electrocardiogram (Triplicate)	_____
Tumor Biopsy (ies) (From consent to Day -1)	_____

Week 1

Subject Assessment	_____
Pregnancy Test (if appropriate)	_____
Weight	_____
Vital Signs	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Amylase and Lipase	_____
CA 19-9 and/or CEA	_____
Research Serum Samples	_____
MVA-BN-CV301, (Bevacizumab)	_____
Capecitabine	_____

Week 3

Subject Assessment	_____
Weight	_____
Vital Signs	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Amylase and Lipase	_____
Electrocardiogram	_____
Durvalumab, (Bevacizumab)	_____

Week 5

Subject Assessment	_____
Weight	_____
Vital Signs	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Amylase and Lipase	_____
CA 19-9 and/or CEA	_____
Durvalumab, MVA-BN-CV301, (Bevacizumab)	_____
Capecitabine	_____

Week 6

PT/INR, PTT	_____
Tumor Biopsy (ies)	_____

Week 7

Subject Assessment	_____
Weight	_____
Vital Signs	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Amylase and Lipase	_____
Electrocardiogram	_____
Durvalumab, (Bevacizumab)	_____

Every 8 Weeks, Week 8 Until Progression (Week 8)

Radiology Evaluation and Tumor Measurements	_____

Week 9

Subject Assessment	_____
Weight	_____
Vital Signs	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Amylase and Lipase	_____
TSH (Reflex Free T4 and Total T3 if TSH abnormal)	_____
Urinalysis	_____
CA 19-9 and/or CEA	_____
Electrocardiogram	_____
Research Serum Samples	_____
Durvalumab, FPV-CV301, (Bevacizumab)	_____
Capecitabine	_____

Every 2 weeks, Week 11 Until Progression (Week 11)

Weight	_____
Vital Signs	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Durvalumab, (Bevacizumab)	_____

Every 4 Weeks, Week 13 Until Progression (Week 13)

Subject Assessment	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
Amylase and Lipase	_____
CA 19-9 and/or CEA	_____
Capecitabine	_____

Every 2 weeks, Week 11 Until Progression (Week 13)

Weight	_____
Vital Signs	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Durvalumab, (Bevacizumab)	_____

Every 2 weeks, Week 11 Until Progression (Week 15)

Weight	_____
Vital Signs	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Durvalumab, (Bevacizumab)	_____

Every 8 Weeks, Week 8 Until Progression (Week 16)

Radiology Evaluation and Tumor Measurements	_____

Every 4 Weeks, Week 13 Until Progression (Week 17 Onward)

Subject Assessment	_____
Concurrent Medications	_____
Adverse Event Evaluation	_____
History and Physical	_____
Performance Status	_____
Amylase and Lipase	_____
CA 19-9 and/or CEA	_____
Capecitabine	_____

Every 2 weeks, Week 11 Until Progression (Week 17 Onward)

Weight	_____
Vital Signs	_____
CBC with Differential	_____
Serum Chemistries	_____
Magnesium	_____
Durvalumab, (Bevacizumab)	_____

Every 8 Weeks, Week 17 Until Progression

Urinalysis	_____
TSH (Reflex Free T4 and Total T3 if TSH abnormal)	_____
Research Serum Samples	_____

Week 17
FPV-CV301 _____
Research Serum Samples _____

Week 21
FPV-CV301 _____

Weeks 25 and 37
FPV-CV301 _____

Every 24 weeks, Week 53 until progression
FPV-CV301 _____

Week 49
Research Serum Samples _____

Off Study
Subject Assessment _____
Weight _____
Vital Signs _____
Concurrent Medications _____
Adverse Event Evaluation _____
History and Physical _____
Performance Status _____
Adverse Events Evaluation _____
CBC with Differential _____
Serum Chemistries _____
Magnesium _____
Amylase and Lipase _____
TSH (Reflex Free T4 and Total T3 if TSH abnormal)_____
Research Serum Samples _____
CA 19-9 and/or CEA _____
Radiology Evaluation and Tumor Measurements _____
Electrocardiogram _____

Follow-up Assessments
Survival, post-trial therapy _____

5. SAFETY VARIABLES AND TOXICITY ASSESSMENT

The Principal Investigator or Sub-investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf

5.1. Adverse Events Assessment

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

The following will be detailed further below, but these guidelines are meant as an important summary to adverse event definition, and reporting rules for this protocol:

- Adverse events of special interest: An adverse event of special interest (AESI) for durvalumab and for the combination of agents in this study include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy.
    - Not all AESIs are Serious Adverse Events (SAEs)
    - All AESIs should be reported to **Astra Zeneca and Bavarian Nordic** within 24 hours

- Serious Adverse Events: A serious adverse event (SAE) is any adverse event which could result/has resulted in a subject's death, hospitalization/prolongation of hospitalization, significant disability/incapacity, the need for urgent medical or surgical intervention, or birth defects/spontaneous abortion.
    - Not all SAEs are AESIs
    - Only "reportable" serious adverse events will be reported. "Reportable" is defined as any SAE that is unexpected (i.e. not among the known adverse events associated with the therapies used or with the study procedures performed) or is possibly, probably, or definitely related to the therapy. ***Each site is required to follow their local policies for reporting SAEs to their local IRB.***
    - All SAEs must be reported to Astra Zeneca
    - Only ***unexpected*** SAEs that are possibly, probably, or definitely related to the therapy (any part of the combination) should be reported to the Georgetown DSMC, and to the FDA

5.2. Study Monitoring

Data safety monitoring committee (DSMC)

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

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

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

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 3 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

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

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

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

Of note, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. The Multicenter Project Management Office will be tasked with the job of collecting all primary source documentation for patients enrolled outside of Georgetown University. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review. Faxed records should be sent to 202-687-3821 with an email to the Multicenter Project Managers and Dr. Weinberg to confirm receipt of those records.

5.3. Adverse Events and Toxicity Definitions

5.3.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events. The term AE is used to include both serious and non-serious AEs.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of the investigational product) or non-treatment emergent. A non-treatment emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.*, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

5.3.2. Serious Adverse Events

1) **Death of Subject** an event that results in the death of a subject.
2) **Life-Threatening** an event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
3) **Hospitalization or**
4) **Prolongation of Hospitalization** an event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** an anomaly detected at or after birth, or any anomaly that results in fetal loss.
6) **Persistent or Significant Disability/Incapacity** an event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
8) **Spontaneous Abortion** Miscarriage experienced by study subject.
9) **Elective Abortion** Elective abortion performed on study subject.

5.3.3. Adverse Event Severity

The study investigator will rate the severity of each adverse event according to the NCI CTCAE Version 4.0. For adverse events not captured by the NCI CTCAE Version 4.0, the following should be used:

1) **Grade 1 (Mild)** The adverse event is transient and easily tolerated by the subject.
2) **Grade 2 (Moderate)** The adverse event causes the subject discomfort and interrupts the subject's usual activities.

3) **Grade 3/4 (Severe or Life Threatening)** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

4) **Grade 5 (Severe, resulting in Death)** The adverse event resulted in death of the subject.

5.3.4. Relationship to Study Drugs

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug(s).

1) **Definitely Related** An adverse event has a clear temporal relationship to study drug(s) and/or recurs on re-challenge and an Other cause of event is extremely unlikely.

2) **Probably Related** An adverse event has a strong temporal relationship to study drug(s) or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.

3) **Possibly Related** An adverse event has a strong temporal relationship to the study drug(s) and an Other cause of event is equally or less likely compared to the potential relationship to study drug.

4) **Probably Not Related** An adverse event has little or no temporal relationship to the study drug(s) and/or a more likely Other cause of event exists.

5) **Not Related** An adverse event is due to an underlying or concurrent illness or effect of another drug(s) and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

If an investigator's opinion of possibly, probably not, or not related to study drug(s) is given, an Other cause of event must be provided by the investigator for the serious adverse event.

Special consideration must be taken into consideration as to *which study drug(s)* the adverse event is linked to. If this is not known, or cannot be stated definitively, then the investigator should not the relationship to “study regimen” – or similar language that links the AE to any/all of the therapies

It is important to note:

- ***Not all SAEs are AESIs***
- ***Only “reportable” serious adverse events will be reported. “Reportable” is defined as any SAE that is unexpected (i.e. not among the known adverse events associated with the therapies used or with the study procedures performed) or is possibly, probably, or definitely related to the therapy. Each site is required to follow their local policies for reporting SAEs to their local IRB.***
- ***All SAEs must be reported to Astra Zeneca and to Bavarian Nordic***
- ***Only unexpected SAEs that are possibly, probably, or definitely related to the therapy (any part of the combination) should be reported to the Georgetown DSMC, and to the FDA***

5.3.5. Non-Serious Adverse Events of Special Interest (Immediately Reportable)

5.3.5.1 Definition of Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

It is important to note:

- ***Not all AESIs are Serious Adverse Events (SAEs)***
- ***All AESIs should be reported to Astra Zeneca and to Bavarian Nordic within 24 hours***

5.3.5.2 Reportable AESIs

AESIs for durvalumab and for the combination of agents in this study include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. Many of these AESIs are being monitored for the potential as immune-related adverse events.

An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Chair or Co-Chair.

5.3.5.3 Specific AESIs

Adverse events of special interest for this study include the following:

- In general, conditions (***regardless of Grade***) suggestive of an autoimmune disorder, including but not limited to hepatitis, pneumonitis, colitis, endocrinopathies, pancreatitis (clinical OR asymptomatic increased serum lipase or increased serum amylase), thyroiditis, rheumatoid arthritis, Type I diabetes, vasculitis, neuritis, systemic lupus erythematosus, Sjögren's syndrome, and multiple sclerosis.
    - For patients with Grade 1 laboratory abnormalities at baseline that were NOT exclusionary, an AESI would be defined as any INCREASE in the Grade of lab abnormality
        - E.g. – for a patient with Grade 1 AST at study entry (not exclusionary), an AESI would be defined if the AST increased to Grade 2
- Grade ≥ 2 events suggestive of hypersensitivity, cytokine release, systemic inflammatory response, or infusion reaction syndromes, including but not limited to influenza-like illness, fever, chills, rash, urticaria, dyspnea, wheezing, angioedema, tachycardia, and hypotension occurring within 24 hours of the end of the infusion.
- Grade ≥ 2 events suggestive of cytokine release syndrome (occurring ≥ 24 hours after the end of the infusion), including but not limited to influenza-like illness, nausea, headache, fevers, chills, tachycardia, hypotension, and shortness of breath.
- Grade ≥ 3 acute infection (bacterial, viral, zoonotic, or fungal)
- Grade ≥ 2 rash, vitiligo, or pruritus (concern for dermatitis)
- Grade ≥ 2 diarrhea (concern for colitis)
- Grade ≥ 2 hypoxia or dyspnea (concern for pneumonitis)
- Grade ≥ 2 pleural effusion
- Grade ≥ 2 pericardial effusion
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Nephritis

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure [2].

5.3.5.4 Criteria for Hy's Law (FDA Guidance 2009)
The drug causes hepatocellular injury, generally shown by a higher incidence of 3 fold or greater elevations above the ULN of ALT or AST than the (non hepatotoxic) control drug or placebo

Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

5.4. Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded in the source documentations (such as the electronic medical record system) and/or patient study chart using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets the definition of a reportable finding.
The following variables will be collected for each AE:

- AE (verbatim)
- Description of AE
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- For an AE that is an AESI or SAE, a specific notation will be made
- Separate Investigator causality ratings against durvalumab (yes or no) and/or CV301, and/or capecitabine, and/or bevacizumab (for colorectal cancer patients) OR to a study procedure
- Action taken with regards to any/all of the study agents (listed above)
- Outcome

In addition, the following variables will be collected for AESIs and SAEs, as applicable:

- Date the AE met criteria for an AESIs or SAEs
- Date Investigator became aware of the AESIs or SAEs
- Reason the AE qualified as an AESIs or SAEs
- Date of hospitalization (if applicable)
- Date of discharge (if applicable)
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)

5.5. Adverse Event Collection Period

All adverse events are reported from the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab, CV301, capecitabine, or bevacizumab – whichever is given last as part of the clinical trial (patients who continue capecitabine or bevacizumab as part of standard of care, the reporting period is ONLY 90 days after the last dose given on study) or until the initiation of alternative anticancer therapy.

OF NOTE: For the time between when consent is obtained, and the first dose of therapy is given, AESIs and SAEs are only reported if the event is related to a study procedure.

During the course of the study all AEs, AESIs, and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related AESIs or SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all AESIs or SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

In addition, all AESIs or SAEs related to protocol requirements will be collected from the time the subject signed the study-specific informed consent. This could include, for example, AESIs or SAEs associated with study-required biopsies prior to initiating study medications. However, AESIs and SAEs that are unrelated to any study events (for example a hospitalization related to the underlying disease that occurs prior to initiating study medications) do not need to be reported. Any questions or uncertainties should be directed to the Study Chairs.

5.6. Adverse Event Reporting

All AESIs will be reported to Astra Zeneca and to Bavarian Nordic within 24 hours.

Only "reportable" SAEs will be reported. "Reportable" is defined as any SAE that is unexpected (i.e. not among the known adverse events associated with the therapies used or with the study procedures performed) or is possibly, probably, or definitely related to the therapy. ***Each site is required to follow their local policies for reporting SAEs to their local IRB.***

All "reportable" SAEs must be reported within 24 hours to Astra Zeneca and to Bavarian Nordic.

Only ***unexpected*** SAEs that are possibly, probably, or definitely related to the therapy (any part of the combination) should be reported to the Georgetown DSMC, and to the FDA

For patients enrolled outside of Georgetown University, all supporting documentation for SAEs that need to be reported to the Georgetown IRB will be sent (faxed or HIPPA compliant email) to the Multicenter Project Management Office and to the Study Chair, Dr. Pishvaian within 24 hours. Faxed records should be sent to 202-687-3821, with an email to the Multicenter Project Managers, Dr. Weinberg (benjamin.a.weinberg@gunet.georgetown.edu), and Dr. Pishvaian (pishvaim@georgetown.edu) to confirm receipt of those records.

The adverse event (AESI or SAE) report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included.

For AEs that require reporting to the FDA (Unexpected SAEs related to therapy only) or Astra Zeneca / Bavarian Nordic (AESIs or SAEs), reporting will occur via a MedWatch/AdEERs form, in accordance with the reporting obligations of 21 CFR 312.32. For AEs that must be reported to AstraZeneca and Bavarian Nordic., a copy of the MedWatch/AdEERs report must be faxed or emailed to AstraZeneca and Bavarian Nordic at the time the event is reported to the FDA. It is the responsibility of the sponsor (Georgetown) to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca and Bavarian Nordic at the same time.

A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number **(ESR-14-10067)**
- The investigator must note if the AE is an AESI, SAE, or unexpected SAE related to therapy
- The investigator must also indicate, either in the adverse event report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the adverse event is ***related to disease progression***, as determined by the investigator.
- ***Send the AE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com
- ***Send the AE report and accompanying cover page by way of email to Bavarian Nordic's designated mailbox:*** drug.safety@bavarian-nordic.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the IRB, AstraZeneca, Bavarian Nordic and the FDA, as detailed above.

5.7. Pregnancy

In the event of a positive pregnancy test result, study drugs will be immediately discontinued. The investigator must report the positive pregnancy test within 1 working day of the site becoming aware of the pregnancy to the local and the Georgetown IRB. Patients should also notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within five days after the treatment period. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected, and the status of the mother and child should be reported to the local and the Georgetown IRB after delivery. Male subjects should also notify the investigators if the subject's partner should become pregnant during the study, this should also be reported within 1 working day of site awareness.

5.7.1. Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

5.7.2. Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or CV301. Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented. Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must

obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

5.8. Overdose

An overdose is defined as a subject receiving a dose of study medication in excess of that specified in the protocol.

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor (Georgetown) and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (AEMailboxClinicalTrialTCS@astrazeneca.com). If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab. The investigator will use clinical judgment to treat any overdose.

5.9. 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 in the sections above.

5.10. Hepatic Function Abnormality

Hepatic function abnormality (*defined as a worsening over baseline in total bilirubin, AST, or ALT*) in a study subject, with or without associated clinical manifestations, *and of any grade* is required to be reported as an AESI *within 24 hours of knowledge of the event* to AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (AEMailboxClinicalTrialTCS@astrazeneca.com).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

5.11. Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the Study Chair and in accordance with the Georgetown IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects.

5.12. Toxicity Management (See Appendix E)

Importantly, the dose of capecitabine parallels the dose used in the "maintenance" setting for pancreatic cancer[3]. However, for colorectal cancer, the dose of capecitabine in the CAIRO 3 trial was higher –

625mg/m^2 continuously daily [4]. In our experience, that dose given chronically can lead to significant toxicities and is not ideally suited for the “maintenance” setting.

Dose modifications or adjustments for capecitabine and bevacizumab are detailed below. There will be no dose modifications or adjustments for durvalumab. Patients who experience significant toxicities requiring holding durvalumab will be allowed symptomatic care, followed by a re-challenge of durvalumab, as detailed below. There will be no dose modifications of the CV301 doses.

5.12.1. Management of Toxicities Related to Capecitabine

Capecitabine dosing will be 1000mg orally twice a day, Monday – Friday weekly. Common toxicities associated with capecitabine include nausea, vomiting, myelosuppression, stomatitis, and hand-foot syndrome, though at these maintenance doses, those AEs are less common. For patients who experience AEs that are clearly attributable in the investigators opinion to capecitabine, the following dose adjustments can be made.

	Adverse Event	First Occurrence	Second Occurrence	Third Occurrence
Hematologic Toxicity	• Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/uL) lasting ≥ 7 days • Grade ≥ 3 febrile neutropenia • Grade ≥ 4 anemia • Grade ≥ 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with clinically significant bleeding	1. Hold all therapy and check CBC weekly until recovery to: ANC ≥1000/mL, Platelets ≥75000/mL, and HgB ≥8g/dL AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	1. Hold all therapy and check CBC weekly until recovery to: ANC ≥1000/mL, Platelets ≥75000/mL, and HgB ≥8g/dL AND 2. Decrease Capecitabine to 500mg QAM, and 500mg QPM	**Discontinue Capecitabine**
	ANC≥500/ml but <1000/mL OR Platelets ≥75000/ml but <100000/mL	1. Hold all therapy and check CBC weekly until recovery to: ANC ≥1000/mL, Platelets ≥75000/mL, and HgB ≥8g/dL AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	1. Hold all therapy and check CBC weekly until recovery to: ANC ≥1000/mL, Platelets ≥75000/mL, and HgB ≥8g/dL AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	**Discontinue Capecitabine**
	ANC ≥1000/ml but <1500/mL OR Platelets ≥75000/ml but <100000/mL	1. Continue therapy AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	1. Continue therapy AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	**Discontinue Capecitabine**
Non-Hematologic Toxicity	Nausea/Vomiting CTC ≥ Grade 3 despite optimal anti-emetic therapy	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND 2. Decrease Capecitabine to 500mg QAM, and 500mg QPM	**Discontinue Capecitabine**
	Diarrhea CTC ≥ Grade 3, despite optimal antidiarrheal therapy OR Fatigue CTC ≥ Grade 3 OR Mucositis CTC ≥ Grade 3 OR Other Toxicity Not Defined Herein CTC ≥ Grade 3 despite optimal supportive care	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND 2. Decrease Capecitabine to 500mg QAM, and 500mg QPM	**Discontinue Capecitabine**
Capecitabine-Specific Toxicity	Hand-Foot syndrome CTC ≥ Grade 3	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND 2. Decrease Capecitabine to 1000mg QAM, and 500mg QPM	1. Hold all therapy until recovery to Grade 1 (or Grade 2 level, if present at baseline) AND 2. Decrease Capecitabine to 500mg QAM, and 500mg QPM	**Discontinue Capecitabine**

If capecitabine doses need to be held for toxicity related to capecitabine, all other study medications may continue.

Table 6: Capecitabine Dose Adjustments

5.12.2. Management of Toxicities Related to Bevacizumab

Bevacizumab dosing will be 5mg/kg IV q2weeks. Toxicities attributable strictly to bevacizumab are uncommon, but known toxicities include proteinuria, bowel perforation, and arterial

thromboembolism. Bevacizumab can also enhance thrombocytopenia. There will be no dose adjustments for bevacizumab. Bevacizumab will be HELD for the following:

- Grade 2 or 3 proteinuria
- Grade ≥ 3 hypertension

The bevacizumab may be resumed if these AEs resolve to Grade ≤1, with medical intervention as necessary.

Patients who experience the following AEs that are clearly attributable in the investigators opinion to bevacizumab, the bevacizumab will simply be discontinued altogether:

- Any Grade of bowel perforation
- Grade 4 proteinuria
- Any arterial thromboembolism

5.12.3. General Management of Immune-Related Toxicities (Additional Details Provided in Appendix E, Below)

5.12.3.1. Infusion-Related Reactions

Because durvalumab is a monoclonal antibody and targets the tumor cell-immune cell interaction, infusion-related reactions associated with hypersensitivity reactions, target-mediated cytokine release, and/or emergent anti-therapeutic antibodies may occur.

To minimize the risk and sequelae of infusion-related reactions, the initial dose of durvalumab will be administered over 90 minutes followed by a 90-minute observation period and subsequent infusion times will be shortened to 60 minutes only if the initial dose administration is well tolerated.

5.12.3.2. Cytokine Release Syndrome

Cytokine release as a result of T-cell activation is a theoretical response to durvalumab. Mild flu-like symptoms such as fever, headache, and myalgias may occur following infusion (hours to days). In contrast, severe, exaggerated cytokine release is not anticipated in response to durvalumab.

Mild to moderate presentations of CRS may be treated symptomatically with analgesics, anti-pyretics, antihistamines and IV fluids as indicated. Severe or life-threatening presentations of CRS, such as hypotension not responsive to initial IV fluid bolus, tachycardia, dyspnea or chest discomfort should be treated aggressively with supportive and resuscitative measures as indicated, including the use of high dose corticosteroids, IV fluids, and other supportive measures.

5.12.3.3. Gastrointestinal Toxicity

Gastrointestinal toxicity, including autoimmune colitis, has been observed with immunomodulatory agents targeting the PD-L1/PD-1 pathways. Gastrointestinal toxicity is a potential risk for durvalumab, and the risk of gastrointestinal toxicity with the combination of durvalumab and CV301 is unknown. Patients with known history of active inflammatory bowel diseases, including those with small or large intestine inflammation, such as Crohn's disease or ulcerative colitis, will be excluded from the study.

Diarrhea (defined as either first watery stool or an increase in frequency of 50% above baseline with urgency or nocturnal bowel movement or bloody stool) should be further

evaluated, and infectious or alternate etiologies should be ruled out. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. All patients with confirmed colitis should also have an ophthalmic examination, including a slit lamp examination, to rule out uveitis.

Study treatment should be interrupted for patients who develop Grade ≥ 2 diarrhea and the use of corticosteroids should be considered. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered off (i.e., to a prednisone dose ≤10 mg/day or equivalent). Patients with colitis should also discontinue any non-steroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms.

Patients who resume treatment should be monitored closely for signs of renewed diarrhea.

5.12.3.4. Hepatotoxicity

Hepatotoxicity has been observed with immunomodulatory agents targeting the PD-L1/PD-1 pathways. Hepatitis is a potential risk of durvalumab. The risk of hepatotoxicity with the combination of durvalumab and CV301 is unknown.

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment. Patients with documented liver metastases are eligible for enrollment but must have AST and ALT values ≤ 2.5X ULN at screening. Patients with known liver disease that could increase susceptibility to or exacerbate the impact of any potential hepatotoxicity of study treatment, including those with active hepatitis B or active HCV infection will be excluded from the study.

While on this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed within 24 hours of presentation and reviewed before administration of the next dose of study drug.

If increased LFTs are observed, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and bile duct should be performed to rule out neoplastic or other causes for the increased LFTs. Liver biopsy should be considered and anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-LKM, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to the following guidelines (Table 10). For patients with elevated LFTs at baseline due to documented liver metastases, further elevation of LFTs may not require dose interruptions if there are no progressive changes in the ALT and/or AST (i.e., less than a doubling) and if there are no progressive elevations in total bilirubin or PT/INR.

AST/ALT > ULN to 3X ULN with total bilirubin ≤ 2X ULN OR AST/ALT rises > 3–fold baseline	Continue durvalumab and FPV-CV301 Monitor LFTs weekly
AST/ALT >3X ULN to <5X ULN with total bilirubin ≤ 2X ULN	HOLD durvalumab and FPV-CV301 Monitor LFTs weekly Restart durvalumab and FPV-CV301 if AST/ALT ≤3X ULN with total bilirubin ≤2X ULN
AST/ALT >5X ULN with total bilirubin ≤ 2X ULN	HOLD durvalumab and FPV-CV301 Consider administering high dose IV steroids (e.g., methylprednisolone) for 24-48 hours followed by prednisone 1-2 mg/kg/day (or equivalent) with taper over 1 month; consider liver biopsy prior to initiation of steroids If LFTs do not decrease within 48 hours after initiation of systemic steroids, consider addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFa antagonist) to the corticosteroid regimen Monitor LFTs every 48-72 hours until decreasing, and then follow weekly Restart durvalumab and FPV-CV301 if AST/ALT ≤3X ULN with total bilirubin ≤2X ULN Permanently discontinue the durvalumab and FPV-CV301 for life threatening immune related hepatic events
AST/ALT > ULN with total bilirubin > 2X ULN	HOLD durvalumab and FPV-CV301 Consider administering high dose IV steroids (e.g., methylprednisolone) for 24-48 hours followed by prednisone 1-2 mg/kg/day (or equivalent) with taper over 1 month; consider liver biopsy prior to initiation of steroids If LFTs do not decrease within 48 hours after initiation of systemic steroids, consider addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFa antagonist) to the corticosteroid regimen Monitor LFTs every 48-72 hours until decreasing, and then follow weekly Restart durvalumab and FPV-CV301 if AST/ALT ≤3X ULN with total bilirubin ≤2X ULN Permanently discontinue the durvalumab and FPV-CV301 for life threatening immune related hepatic events

Table 7: Management of Hepatotoxicity

5.12.3.5. Dermatologic Toxicity

Dermatologic toxicity has been observed with immunomodulatory agents targeting the PD-L1/PD-1 pathways, and is a potential risk of durvalumab. The risk of dermatologic toxicity with the combination of durvalumab and CV301 is unknown.

Patients with a rash can be treated with antihistamines and topical steroids. If the rash is ≥Grade 2, then a dermatologist should be consulted. If the rash is ≥ Grade 3, the durvalumab and CV301 should be held, and oral prednisone (e.g. 10mg/day or equivalent) can be administered. The durvalumab and CV301 may be restarted if the rash resolves to ≤ Grade 1 and systemic steroid dose is prednisone ≤ 10 mg/day or equivalent. The durvalumab and

CV301 should be permanently discontinued for life threatening immune-related dermatologic toxicity.

5.12.3.6. Endocrine Toxicity

Endocrine toxicity has been observed with immunomodulatory agents targeting the PD-L1/PD-1 pathways, and is a potential risk of durvalumab. The risk of endocrine toxicity with the combination of durvalumab and CV301 is unknown.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected.

TSH and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Patients who are found to have asymptomatic elevations in the TSH may continue the durvalumab and CV301, and be started on thyroid hormone replacement therapy. If the hypothyroidism is symptomatic, the durvalumab and CV301 should be held, and thyroid hormone replacement therapy started until the TSH is normal, in which case the durvalumab and CV301 may be restarted.

5.12.3.7. Ocular Toxicity

Ocular toxicity has been observed with immunomodulatory agents targeting the PD-L1/PD-1 pathways, and is a potential risk of durvalumab. The risk of ocular toxicity with the combination of durvalumab and CV301 is unknown.

An ophthalmologist should evaluate ocular complaints with an examination of the conjunctiva, anterior and posterior chambers, and retina; visual field testing and an electroretinogram should also be performed. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Patients in the study are encouraged to maintain eye hydration, generally through the use of moisturizing eye drops. In the event of symptomatic autoimmune uveitis, iritis, or episcleritis, the durvalumab and CV301 should be held until resolution of the autoimmune reaction (with topical steroids if necessary), in which case the durvalumab and CV301 may be restarted. The durvalumab and CV301 should be permanently discontinued if topical therapy is insufficient for controlling the autoimmune opthamologic toxicities.

5.12.3.8. Pulmonary Toxicity

Pulmonary toxicity has been observed with immunomodulatory agents targeting the PD-L1/PD-1 pathways, and is a potential risk of durvalumab. The risk of pulmonary toxicity with the combination of durvalumab and CV301 is unknown.

Patients with known history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan will be excluded from the study.

Patients will be assessed for pulmonary signs and symptoms such as dyspnea, cough, fatigue, and hypoxia throughout the study. Patients will also have CT scans of the chest at every tumor assessment and any new pulmonary infiltrates should be assessed. Workup of pulmonary adverse events may include, as appropriate:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy

- Pulmonary function testing (with diffusion capacity of lung carbon monoxide)

Alternative causes of pulmonary adverse events (e.g., lymphangitic carcinomatosis, infection, heart failure, or chronic obstructive pulmonary disease) should be explored in parallel. Treatment should be dictated by clinical severity and may include administration of steroids and oxygen. Consultation with a pulmonologist is appropriate for a suspected lung immune-related adverse events, and a biopsy should be strongly considered prior to the administration of steroids.

Study treatment should be interrupted for patients who develop Grade ≥ 2 dyspnea or hypoxia, and a pulmonologist should be consulted before consideration of systemic steroids. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered off (i.e., to a prednisone dose ≤10 mg/day or equivalent). The durvalumab and CV301 should be permanently discontinued in the event of life-threatening pulmonary toxicity.

Grade 1 (Asymptomatic, clinical or diagnostic, e.g. radiographic observations only, intervention not indicated)	Continue durvalumab and FPV-CV301 - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	HOLD durvalumab and FPV-CV301 until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment. - Monitor symptoms daily and consider hospitalization - Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent) - Reimaging as clinically indicated - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started - If still no improvement within 3-5 days despite IV methylprednisone at 2-4m4mg/kg/day, promptly start immunosuppressive therapy (infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation) - Consider pulmonary and infectious disease consult - Consider as necessary discussing with study physician
Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	PERMANENTLY DISCONTINUE DURVALUMAB AND FPV-CV301 - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain pulmonary and infectious disease consult - Hospitalize the patient - Supportive Care (oxygen, etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections

Table 8: Management of Pulmonary Toxicity

6. MEASUREMENT OF EFFECT

6.1. Assessment Parameters

Response and progression will be evaluated in this study using RECIST 1.1 Criteria, as well as modified RECIST (both detailed below). Response assessment data, disease control rate, PFS, and OS will be summarized for all patients with measurable disease by dose level or tumor type, when appropriate. Objective response is defined as a CR or PR, as determined by investigator assessment and confirmed by repeat assessment ≥ 4 weeks after initial documentation. Patients with missing baseline or no additional response assessments will be classified as non-responders. Among patients with an objective response, duration of objective response will be defined as the time from the initial complete or partial response to the time of disease progression or death, whichever occurs first. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment. PFS is defined as the time from the first day of study treatment (Week 1, Day 1) until documented disease progression or death, whichever occurs first. For patients who do not have documented progressive disease or death before the end of the study or who are lost to follow-up, PFS will be censored at the day of the last tumor assessment. OS is defined as the time from the first dose of study treatment to the time of death from any cause. For patients who do not die before the end of the study or who are lost to follow-up, OS will be censored at the date of last contact.

6.1.1. Definitions

Evaluable for toxicity: Patients must have received at least one dose of CV301 and durvalumab to be assessable for toxicity. Patients who are taken off study prior to receiving the first dose of durvalumab will need to be replaced.

Evaluable for objective response: Any patient who initiates study medications, and is taken off study prior to 8.5 months (colorectal cancer) or 4 months (pancreatic cancer) for disease progression or clinical progression, including death related to the underlying pancreatic or colorectal cancer (as determined by the treating oncologist) will be considered efficacy evaluable. However, patients who have initiated study medications, and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed related to their underlying pancreatic or colorectal cancer will not be considered evaluable for efficacy. These patients will need to be replaced for the efficacy analysis. Reasons for patients who have initiated study medications, but are no longer evaluable could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping therapy
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying pancreatic or colorectal cancer
- An unexpected trauma or death that is considered unrelated to the underlying pancreatic or colorectal cancer

Patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of week 8 will also be considered evaluable.)

6.2. Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

6.2.1. Disease Parameters

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

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan; or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), peritoneal carcinomatosis, and cystic lesions are all non-measurable.

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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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 or absence of each should be noted throughout follow-up.

6.2.2. Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

6.2.3. Response Criteria

6.2.3.1. Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions. Partial responses may be claimed if these criteria are met at a subsequent time point ≥ 4 weeks later.

Progressive Disease (PD)
At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.2.3.2. Evaluation of Non-Target Lesions
Complete Response (CR)
Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD)
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

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

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

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

6.2.4. RECIST 1.1 Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	>4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	>4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once >4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.				

Table 9: Response Evaluation. Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.3. Modified Response Evaluation Criteria in Solid Tumors (RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment. Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (v1.1) conventions and immune-related response criteria (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

	RECIST 1.1	**Modified RECIST**
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥ 20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥4 weeks from the date first documented

Table 10: Differences Between RECIST 1.1 and Modified RECIST

6.3.1. Impact of Non-target Lesion Response on Modified RECIST

The assessment of non-target lesions will be captured at each timepoint using standard RECIST 1.1 definitions of CR, non-CR/non-PD, and PD. However, in determining the overall modified RECIST tumor response, non-target lesions contribute only to the assessment of a complete response. Non-target lesions are not considered in the overall definition of PR, SC, or PD per modified RECIST.

6.3.2. Impact of New Lesions on Modified RECIST

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

6.4. Definition of Disease Progression

Disease response/progression will be assessed according to RECIST 1.1, as detailed above. However, RECIST 1.1 will be adapted to account for the potential of pseudoprogression, in which immune-mediated tumor infiltration may lead to an initial increase in the size of the tumors, and can lead to a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, standard RECIST 1.1 criteria may not provide an accurate response assessment of immunotherapeutic agents such as durvalumab and CV301. Therefore, for defining disease progression, RECIST 1.1 will be used with the following adaptations that take into account Modified RECIST, as detailed above:

If radiologic imaging shows initial PD, as defined by RECIST 1.1, but patients are adequately tolerating therapy, patients may continue therapy until the next restaging while awaiting radiologic confirmation of progression. The decision to continue therapy should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease:
If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy.

7. STATISTICAL CONSIDERATIONS

7.1. Study Design

This is a dual arm, open label phase II study to evaluate the safety and clinical activity of the combination of durvalumab with CV301 for patients with metastatic colorectal or pancreatic cancer whose disease is stable on, or responding to 1st line therapy for metastatic disease. Patients with metastatic colorectal or pancreatic adenocarcinoma who still have an adequate performance status and normal hepatic and renal function will be eligible.

The trial will consist of two parallel Phase II trials – one for patients with metastatic colorectal cancer, and one for patients with metastatic pancreatic cancer (Figure 5). Patients will be seen every two weeks through eight weeks, and then routinely every 4 weeks thereafter for as long as the patient is on study. Adverse events will be monitored throughout the trial (safety tests will be performed every 2 weeks for the first 8 weeks, and then every 4 weeks thereafter) and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Restaging studies will be performed every 8 weeks (typically CT scans), by the calendar. Patients whose tumors have not progressed at the time of restaging, and who continue to tolerate treatment will continue on study.

The study is estimated to last 36 months. Patient treatment will continue until disease progression, death, or until the physician or patient request removal from the study for any reason.

7.2. Sample Size Considerations

The trial will use a two-stage Simon Minimax Phase II design[6] in each arm. All patients meeting the eligibility criteria who have signed a consent form, begun treatment, and are not lost to follow-up or who are not taken off study for reasons other than progression or death before 4 months for pancreatic cancer arm or 8.5 months for colorectal cancer arm will be considered evaluable for the 4-month PFS rate for pancreatic cancer arm or for the 8.5 month PFS rate for colorectal cancer arm. We will assume a one-sided alpha level of 0.05 and a power of 80% to test the null hypothesis of PFS rate is at most 50% vs. the alternative hypothesis of PFS rate at least 75% for each arm. In the first stage, 14 patients will be needed. If 7 or fewer of the 14 patients are alive and progression-free at 4 months, we will conclude that this treatment is insufficiently active in this population and terminate the study. If 8 or more of these 14 patients are alive and progression-free at 4 months, we will continue the study to the second stage and accrue a total of 23 evaluable patients. If 15 or fewer of these 23 patients are alive and progression-free at 4 months, we will conclude that this treatment is insufficiently active in this population. If 16 or more of these 23 patients are alive and progression-free at 4 months, this will be considered adequate evidence of efficacy of this treatment and may be recommended for further testing in subsequent studies. Assuming a drop-out rate of 10%, a total of 26 patients for each arm will be accrued in the Phase II portion.

7.3. Efficacy Endpoints

7.3.1. Primary Endpoint

The primary endpoints are the proportion of patients who are progression free at 4 month (PFS_{4mos}) in the pancreatic cancer arm, and the 8.5 months PFS rate in the colorectal cancer arm. PFS is defined as the time from consenting to first disease progression event or death from any cause.

7.3.2. Secondary Endpoints

- Median overall survival (mOS). OS is defined as the time from consenting until death from any cause.

- Objective Response Rate (ORR). ORR is defined as the proportion of patients whose best overall response recorded during treatment is either CR or PR according to the RECIST version 1.1.
    - The duration of response will also be captured as the time from which a response was first identified, until progression of disease (or death due to any cause).
- Disease control rate (DCR). DCR is defined as the proportion of patients with a documented CR, PR, or SD at 4 months according to the RECIST version 1.1.
- Median progression-free survival (mPFS). PFS is defined as the time from consenting to determination of tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first.
- Change in tumor marker (CA 19-9 or CEA) Levels. Will be calculated as absolute change and percentage change from baseline at each assessment using RECIST 1.1 tumor response.

7.3.3. Exploratory Endpoints

- Characteristics of the correlative markers in biopsy and peripheral blood samples

7.4. Analysis Populations

The safety population will consist of all subjects who receive at least 1 dose of durvalumab plus CV301 in combination with maintenance capecitabine and bevacizumab (bevacizumab for the colon cancer patients).

The full analysis population will be used primarily for the analysis of efficacy-related data and will include all subjects who receive at least one dose of durvalumab plus CV301 in combination with maintenance capecitabine and bevacizumab (bevacizumab for the colon cancer patients only).

7.5. Analysis Plan

7.5.1 Demographics Characteristics

Descriptive summaries of demographic characteristics for all enrolled patients will be tabulated. Subjects will be tabulated by cancer type and overall.

7.5.2 Safety Analysis

Safety will be assessed by clinical review of all relevant parameters including adverse events, serious adverse events, laboratory values, vital signs and ECG values. Summary tables and listings will be provided for all reported treatment adverse event by grade,

7.5.3 Efficacy Analysis

We assume that the survival times (PFS and OS) follow exponential distributions.

7.5.4 Analysis for the Primary Endpoint

The Kaplan-Meier method will be used to estimate the PFS at 4 months for the pancreatic cancer arm, and the PFS at 8.5 month for the colorectal cancer arm, and the survival curves will be generated. The PFS rates and their corresponding 95% confidence intervals (CIs) will be presented. The hazard ratio of the PFS and its 95% CI will be presented using Cox regression model.

7.5.5 Analysis for the Secondary Endpoints

OS and PFS will be evaluated using Kaplan-Meier methods. The median OS and PFS and their 95% CIs will be reported and survival curves will be generated based on Kaplan-Meier estimates.

The percentage of subjects with OR and DC will be calculated for each treatment arm with their two-sided 95% CI.

7.5.6 Analysis for the Exploratory Endpoints

The characteristics (high/low; present/absent; specific scoring) of the correlative markers from patient tumor samples and serum will be summarized descriptively by patient, and will take into account the visit/biopsy number. Changes in these characteristics between the pre-treatment collections, and the collections during treatment will be summarized using descriptive statistics.

8. Drug Information, Including Storage and Dispensation

Capecitabine (and bevacizumab for colorectal cancer patients) must be obtained from commercial sources (i.e. they are not provided by the study).

CV301 and durvalumab will be shipped to each individual site once a patient is enrolled. Of note, CV301 will be distributed via our drug depot in Durham, NC. Shipment to and vaccine storage at sites needs to be at -20°C

The order in which the drugs will be administered is based on the fact that the durvalumab can be associated with infusion reactions – whereas the risk of infusion/administration reaction with bevacizumab and CV301 is extremely low. The drugs should be administered:

1) Capecitabine 1000mg PO BID weekly M-F will be ongoing oral administration and can be started at any time on the days of administration of the other agents
2) Durvaluamab
3) Bevacizumab 5mg/kg (Based on weight at screening unless 10% change) IV Q2weeks
   - Bevacizumab should be given IV over 60 minutes for the first two infusions, and then over 30 minutes thereafter
4) MVA-BN-CV301 (prime) - two priming doses of MVA-BN-CV301 which is given s.c. on Day 1 and Day 29. One dose of MVA-BN-CV301 consists of 4 injections of 4 X 10^8 Inf.U in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6 x 10^9 Inf.U per dose.
5) FPV-CV301 (boost) - One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1x10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh on Day 1 of Weeks 9, 13, 17, 21, 25, 37, and q24 weeks starting week 53.

8.1. Durvalumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the investigator as a 500-mg vial solution for infusion after dilution.

8.1.1. Durvalumab Formulation, Packaging, and Storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

8.1.2. Study Drug Preparation

For patients weighing ≥ 30 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W) (based on an average body WT of 75 kg) should be prepared. For subjects <30 kg body weight, dose is determined using body mass. For subjects <30 kg body weight, please contact the Study Chair or Co-chair

8.1.3. Preparation of Durvalumab Doses for Administration with an IV Bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- *24 hours at 2°C to 8°C (36°F to 46°F)*
- *4 hours at room temperature*

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 750mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab (ie, 15.0 mL for 750 mg or 30.0 mL for 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Patient weight at baseline should be used for dosing calculations in patients ≤30 kg unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

8.1.4. Monitoring of Dose Administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study

personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

8.2. CV301

Please refer to the accompanying drug handbooks for CV301 preparation.

8.2.1. MVA-BN-CV301

MVA-mBN336B (common name MVA-BN-CV301 vaccine), is a liquid-frozen, highly attenuated, live recombinant virus based on the viral vector MVA-BN. It is administered as s.c. application. The packages and vials will be labeled according to the respective Product Specifications.

One MVA-BN-CV301 vaccine vial has a nominal titer of 4×10^8 Inf. U in 0.5 mL of the drug product. The specific dose will be determined upon release testing of the drug product and the actual titer upon vaccination will be reported based on results from ongoing stability studies.

One dose of MVA-BN-CV301 consists of 4 injections of 4×10^8 Infectious Units (Inf.U) in 0.5mL (one in each arm, one in each leg). This results in a total administration of 1.6×10^9 Inf.U per dose.

For further details on MVA-BN-CV301 vaccine see current version of the CV301 Investigator's Brochure.

8.2.2. FPV-CV301

FPV-mBN373B (common name FPV-CV301 vaccine), is a liquid-frozen, highly attenuated, live recombinant virus. It is administered as s.c. application. The packages and vials will be labeled according to the respective Product Specifications.

One vaccine dose has a minimum virus titer of 1×10^9 Inf.U FPV-CV301 vaccine in 0.5 mL of the drug product. The specific dose will be determined upon release testing of the drug product and the actual titer upon vaccination will be reported based on results from the ongoing stability studies.

One dose of FPV-CV301 consists of just one 0.5mL injection of at least 1×10^9 Inf.U per 0.5 mL. The vaccine will be injected subcutaneously into the thigh at each dosing timepoint.

For further details on FPV-CV301 vaccine see current version of the CV301 Investigator's Brochure.

8.2.3. Patient Care Implications

Patients should be monitored for 30 minutes after each dose for signs/symptoms of allergic reaction or anaphylaxis. Patients should monitor and report degree and duration of injection site reaction and flu-like symptoms.

9. Correlative Scientific Studies

Please note: Details on collection and shipping, particularly details on the acquisition of supplies and the personnel involved are subject to change. Thus, details on collection and shipping in the Lab Manual are to be considered the most updated (note the Version number and dates).

Serial tumor biopsies will be taken before treatment and after 6 weeks. The levels of immune-inhibitory proteins, including PD-1, PD-L1 (B7H1), B7H3, B7H4, IDO, and arginase will be measured in tumor tissue and their predictive value assessed. The characteristics of the infiltrating T-cells in tumor samples will also be analyzed. In addition, RPMA will be used for phopshoprotein analysis, and tumor samples will be grown *ex vivo* for additional scientific analyses.

This trial will be conducted in conjunction with Dr. Jeffrey Schlom, Chief of the Laboratory of Tumor Immunology and Biology; Dr. James Gulley, Chief of the Genitourinary Malignancies Branch (Head, Immunotherapy Section) in the Center for Cancer Research, NCI, NIH; Dr. Emmanuel (Chip) Petricoin, III with his team at George Mason University; Dr. Jonathan Brody at Thomas Jefferson University; and Dr. Stephen Byers at Georgetown University.

9.1. Tissue Prioritization

Additional details are provided in Appendix C.

9.1.1. Biopsy Tissue Utilization and Prioritization

For the pre-treatment and 6 week biopsy, 6 individual cores will be obtained with an 18-20 gauge needle. The cores will be prepared as follows (and as depicted in Appendix C):

- The first two cores (Correlative sample and phosphoprotein sample) should be placed INDIVIDUALLY in a single standard formalin vials and submitted to the Histopathology and Tissue Shared Resource (HTSR) to be processed into paraffin blocks. The samples from these FFPE block **should not be cut** for an H&E analysis. Rather, the block will be sent in batches to Dr. Schlom at the NIH (First core) and to George Mason University to Dr. Petricoin's lab (second core) for laser capture microdissection of tumor epithelium and stroma for Reverse Phase Protein Microarray (RPPA) analysis.

- The next two cores (Correlative samples) should be placed INDIVIDUALLY in a single cryovials and snap frozen in liquid nitrogen, and stored at -80ºC. These frozen samples will be shipped in batches on dry ice to Dr. Schlom at the NIH.

- The fifth core (organoid sample) will be collected for organoids will be collected in pre-supplied Eppendorf tubes containing Advanced DMEM/F12 (5mL) with Glutamax 1%, Pen/Strep 1%, and HEPES Buffer 1%. Media will be sent to the sites in batches of 10 upon request from Dr. Brody's lab. Samples will be collected, and shipped overnight on WET ice to Dr. Brody's lab.

- The sixth core will be placed in a pre-provided Eppendorf tubes with CRC media with y-compound. This will be shipped on WET ice to the Shared Resources core, c/o Dr. Glasgow, at the Lombardi Cancer Center.

9.1.2. Serial Blood Collection

On week 1, Day 1, Weeks 9, 17, 49 and at the off study visit, 6 green top (Na heparin, 10 mL) tubes and 2 red serum separator (8 mL) tubes will be obtained. Shipping details are provided in Appendix C.

9.1.3. Test Prioritization

There are several correlative markers that will be tested. We do not anticipate that there will be limitations in the samples from blood collection for the flow cytometry analyses or for the assessment of serum soluble factors and cytokine expression profiles. The core biopsy sample collection prioritization is detailed above. In the event that, from the first two cores to be sent to Dr. Schlom's lab, there is insufficient biopsy tissue sample for testing, the following tests prioritization order will be followed (Highest priority is listed first):

1) PD-1
2) PD-L1 (Ventana assay with SP263 antibody)
3) B7H3
4) B7H4
5) CD8
6) CD4
7) FOXPC
8) IDO
9) Arginase
10) Characteristics of the infiltrating T-cells in tumor samples.

9.2. Immune Correlates – Methodology

9.2.1. Peripheral blood Antigen Specific T cell Immune Response

Analysis of antigen-specific responses will be assessed by intracellular cytokine staining (ICS) following a period of in vitro stimulation with overlapping 15-mer peptide pools encoding the tumor-associated antigens (TAAs) CEA, MUC-1, and brachyury. The TAA peptide pools have been designed to contain agonist epitopes that have been previously identified; [7-9] peptide pools encoding for HLA and CEFT (a mixture of CMV, EBV, Flu, and Tetanus toxin) will serve as negative and positive controls, respectively. Peptide mixes will be purchased from JPT (Berlin, Germany), reconstituted in DMSO, and utilized immediately. Cryopreserved PBMC from patients before therapy and at specified time points will be thawed and rested overnight at 37°C, 5% CO_2 in complete media (IMDM supplemented with 10% Human AB, 2mM glutamine, 100 units/ml penicillin, and 100 µg/ml streptomycin). The next day (Day 0), PBMC will be seeded in 12 well plates (2.5 x10^6 in 1 mL), and stimulated with peptide mixes (0.1µg/mL per peptide); cultures will be supplemented on days 3 and 5 with cytokines (IL7 and IL15, 10 ng/mL, PeproTech, Rocky Hill, NJ) and fresh media, and on day 7 will be rested (with removal of cytokines and peptide). On day 11, 1x10^6 cells will be restimulated for 24 hours in 96 well plates with peptide mixes in the presence of anti-CD107a-APC (clone H4A3, BD Biosciences); brefeldin A (1µl/mL) and monensin (0.7µl/mL) (BD Biosciences) will be added to cultures 2 hours after the start of the restimulation and incubated for the final 22 hours. PBMC will then be stained with anti-CD4-PerCP-Cy5.5 (clone OKT4, Biolegend), anti-CD8-AF700 (clone OKT8, Ebioscience), and anti-TNF-PE (clone MAb11), anti-IFNg-PE-Cy7 (clone 4SB3), and anti-IL-2-BV521 (clone 5344.111) (BD Biosciences).

For all flow cytometry experiments, at least 3x10^5 events in the live gate will be acquired with a BD LSR-II flow cytometer equipped with a UV, violet, blue, and red laser. FCS files will be imported and analyzed with FlowJo V.9.7 for Macintosh (TreeStar, Ashland, OR). Fluorescence minus one (FMO) controls will be used for gating, and non-viable cells will be excluded. For ICS experiments, the absolute number of CD4+ or CD8+ lymphocytes producing cytokine or positive for CD107a will be calculated per 1x106 cells plated at the start of the in vitro stimulation (IVS) [10]. The background signal (obtained with the HLA peptide pool), and values obtained prior to therapy will be subtracted from those obtained post-therapy. Values >250 will be scored as positive for TAA-specific immune response following therapy.

9.2.2. Peripheral Blood Mononuclear Cell Subset Analysis

Multicolor flow cytometry will be performed on frozen peripheral blood mononuclear cells (PBMC) as previously described [11]. Staining will be performed using 5 panels (Appendix D, table 1) to identify markers involved in PD-1 signaling (Appendix D, table 2, panel 1), CD4+ T cells, CD8+ T cells, and B cells (Appendix D, table 2, panel 2), Tregs (Appendix D, table 2, panel 3), NKs, NK-T, cDCs, and pDCs (Appendix D, table 2, panel 4), and MDSCs (Appendix D, table 2, panel 5). These panels will identify a total of 123 peripheral immune cell subsets (Appendix D, Table 3), which include 9 parental immune cell types and 114 subsets relating to maturation and function within the parental types. Optimal amounts of antibodies for staining were determined by previous titration experiments. Briefly, 1 million PBMCs per test will be incubated for 15 minutes at 4°C with 2 µL of human TruStain FcX (Biolegend, San Diego, CA) and Live Dead Fixable Stain Blue (Invitrogen, Waltham, MA). Surface antibodies will be added for 30 minutes at 4°C. Cells will then be washed, permeabilized (eBioscience, San Diego, CA), and stained with intracellular antibodies for 30 minutes at room temperature. Samples will be acquired on an LSRII flow cytometer (BD Biosciences, San Jose, CA) equipped with a UV, violet, blue, and red laser, and analyzed using FlowJo V9.7 for Macintosh (Treestar, Ashland, OR). The gating strategy will identify 123 peripheral immune cell subsets, with non-viable cells excluded, and negative gates set based on fluorescence minus one controls. All values will be reported as % of PBMCs in order to help eliminate the bias that could occur in the smaller populations with fluctuations in leukocyte subpopulations [12].

9.2.3. Serum Cytokine and Soluble Factor Analysis

Serum cytokines and soluble factors related to immune regulation will be analyzed using standard ELISA kits for soluble factors, as previously described [13] and cytokines (available via the Inglefield Laboratory, NCI, Frederick using the MesoScale platform (Rockville, MD), V-plex kit).

9.2.4. T Cell Clonal Expansion Assay

cDNA from PBMC will be amplified using locus specific primers for TCR-β. Previously described methods will be used to map the V region and identify the J region [14] and identify clonal sequences of interest. Analytics tools will be used to sort and identify clonal populations of interest in the post- versus pre-treatment samples. Correlation of expansion of a clonal TCR population post treatment will be correlated with clinical outcomes.

9.2.5. Tumor Immunohistochemistry Analysis

We will employ digital immunohistochemistry using MAbs anti-PD-1, anti-PD-L1 (Ventana assay with SP263 antibody), anti-B7H3, and anti-B7H4 along with isotype control MAbs to examine the extent of immune infiltrate in any biopsies collected before treatment and prior to the 2nd dosing of CV301 with durvalumab [86]. We will also employ anti-CD8, anti-CD4, and anti-FOXPC MAbs.

9.2.6. Measurements of Serum Indoleamine 2,3-dioxygenase (IDO)

Tryptophan is catabolized by IDO to N-formylkynurenine which is rapidly converted to kynurenine. Measurement of serum levels of kynurenine and tryptophan can provide evidence of functional IDO activity. Because kynurenine can be further metabolized to downstream products, this assay is not entirely quantitative, but the ratio of tryptophan/kynurenine can provide a relative indication of IDO functional activity. Serum samples from patient taken before treatment and prior to the 2nd dosing of CV301 with durvalumab will be analyzed for kynurenine and tryptophan levels by HPLC. HPLC will be performed according to the method described by Yong, et al [15].

9.2.7. Immunohistochemistry for Detection of IDO in Tissue Samples

Immunohistochemical staining will be performed on 10% formalin fixed, paraffin-embedded tissue sections (4 µm). After deparaffinization and rehydration, the sections will be treated with 0.3% hydrogen peroxide and incubated with 10% bovine serum albumin to block nonspecific staining. The sections will be incubated for 15 minutes at 37°C with proteinase for antigen-retrieval. The sections

will be incubated at room temperature with anti-IDO monoclonal antibody. The sections will then be rinsed and incubated with the biotinylated second antibody. After washing, the sections will be incubated with horseradish peroxidase-conjugated streptavidin, and finally treated with 3,3' diaminobenzidine tetrahydrochloride. The slides will counter stain with Meyer's Hematoxylin [16].

Double immunohistochemical analysis for the detection of CD3+ T-cells in the IDO-stained tissue sections will also be performed using mouse anti-CD3 monoclonal antibodies.

Analyses will be done on biopsies taken before treatment and after 6 weeks on therapy with CV301 with durvalumab.

9.2.8. Measurements of Serum Arginase-1

Arginase is a hydrolase mostly found in liver. It catalyzes the amino acid L-arginine to ornithine and urea. There are two isoforms of arginases, cytoplasmic arginase I and mitochondrial arginase II. Myeloid-derived suppressor cells (MDSC) expressing arginase I deplete L-arginine and profoundly inhibit T-cell functions. Increased levels of MDSC on cancer patients correlated with low L-arginase and high ornithine levels in plasma and T-cell dysfunction.

Serum level of arginase I will be determined by two assays. (a) ELISA kit (BioVendor) using monoclonal antibody to arginase [17] and (b) The function of arginase will be determined by measuring the serum levels of L-arginase and L-ornithine by HPLC [18]. These analyses will be done on samples taken before treatment and after 8 weeks on therapy with CV301 with durvalumab.

9.2.9. Immunohistochemistry for Detection of Arginase-1 in Tissue Samples

Four µm thick sections of the formalin-fixed paraffin-embedded tissue will be stained with polyclonal antibody against arginase I. Double immunohistochemical analysis for the detection of MDSC (CD11b+/CD14- and CD11b+/CD14+) MDSC in the arginase stained tissue sections will also be performed [19].

9.2.10. Reverse Phase Protein Microarray (RPPA)

The Reverse Phase Protein Microarray (RPPA) technology has been developed to address the analytical challenges of the sandwich and forward phase protein arrays (e.g. mismatch of sandwich antibody affinity, imprecision within and between analytes, and poor sensitivity). The platform has been designed to enable non-subjective, quantitative, multiplexed analysis of specific forms of cellular proteins (e.g. phosphorylated, unphosphorylated, and cleaved) from a limited amount of starting sample, such as with a fine needle aspirate or laser capture microdissected (LCM) cellular material to procure pure populations of the target cells of interest. Particularly suited for clinical tissue samples, RPPA uses a single antibody directed against the epitope of interest When coupled to LCM, the RPPA technology can be used to quantifiably measure multiplexed protein phosphorylation changes and total proteins in selected cellular niche (e.g. epithelium and stroma/immune infiltrates).

A key attribute of the RPPA is the ability to quantitatively measure hundreds of signaling proteins concomitantly from only a few thousand cells, thus providing a critical means of broad-scale cell signaling analysis directly from tissue samples, cell culture models, and animal tissues from pre-clinical studies. The RPPA technology, invented in the lab of Drs. Liotta and Petricoin at George Mason University and now optimized for routine clinical sample analysis [20-27], is currently being employed within the CAP/CLIA complaint proteomics laboratory within the Center for Applied Proteomics and Molecular Medicine at George Mason University. No other technology can measure the activity of as many signaling proteins at once from such small amounts of input material.

A selection of peer-reviewed publications contains extensive detailed description of the basic core components RPPA methodology [20-27]. The RPPA format immobilizes an individual test sample in each array spot. An array can be comprised of up to hundreds of patient samples or cellular lysates.

Each array is incubated with a single primary antibody and a single analyte end point is measured. Since RPPAs maintain the concentration of the input sample, the sensitivity is greater as compared with a forward phase, (e.g. antibody array) probed with the same small number of input cells.

With the RPPA technology, serial dilutions are printed of each sample, control or standard, to maintain sample concentration. Each spot contains a bait zone measuring only a few hundred microns in diameter. The detection probe can be tagged and signal amplified independently from the immobilized analyte protein. Coupling the detection antibody with highly sensitive amplification systems can yield detection sensitivities to fewer than 1,000 to 5,000 molecules per spot with good linearity (correlation coefficient or R^2 = 0.990-0.999) and inter-experiment precision (R^2= 0.973). Between run and within run analytical precision is between a 3-13% CV (coefficient of variation).

The RPPA technology has been developed and optimized for performance as a fluorescent-based calibrated assay, generally identical in design and analysis to standard ELISA or standard clinical immunoassays. As a calibrated assay, each assay consists of:

a. Experimental patient samples printed in triplicate two-spot dilutions (neat and 1:4)
b. High, medium, and low controls printed in triplicate two-spot dilutions (neat and 1:4)
c. A calibrator, consisting of a 6-10-point curve whereby the analyte of interest is decreasing in concentration in the background of a constant protein concentration that spans the dynamic range of the analyte in the actual clinical specimen

The analyte concentration is thereby determined by extrapolation to a non-parametrically determined curve fit of the calibration curve and reported in relative fluorescent units (Figure 5, below)

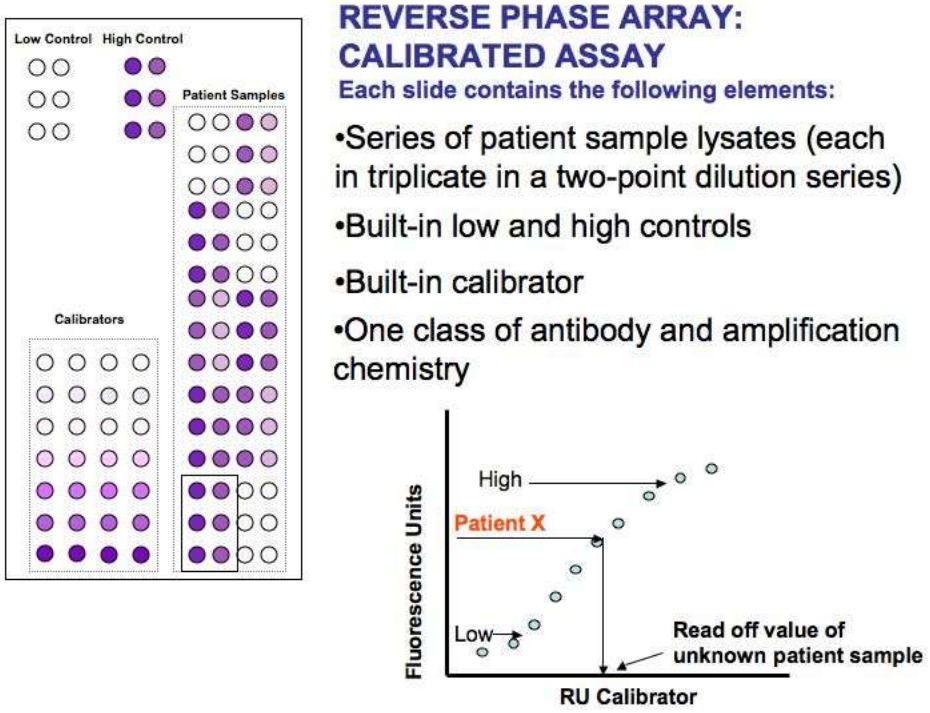


Figure 5. Illustrated schematic of a typical RPPA slide configuration

9.2.10.1. Sample Preparation for Microarray

In order to prepare the sample for arraying, proteins are extracted from the LCM polymer cap as a whole cell lysate using a heated sodium dodecyl sulfate-based lysing solution which produces a denatured lysate suspended in the sample/extraction buffer. The optimal extraction buffer for extracting proteins from tissue cells that have been procured by LCM, with the purpose of performing reverse phase protein arrays, consists of a detergent, denaturing agent and buffer. This buffer is an efficient denaturing extraction buffer for the

extraction and solubilization of cellular proteins from fixed and frozen tissue. An array layout grid is used to determine exact placement of sample and control cell lysates on the printed microarray. Cell lysate solutions for each sample, of a known volume and concentration are loaded into 384 well microtiter plates. Microtiter plates are specifically labeled and loaded into the well plate hotel in the correct order. The RPPA uses slides coated with nitrocellulose. This type of slide is chosen for its high binding capacity, high surface area, minimum effect on protein structure, and intrinsically low background signal. For the printing run, up to 100 slides, (10 slides/platen and 10 platens within the Substrate Hotel), can be loaded into the Aushon 2470 Arrayer at a time.

9.2.10.2. Array Preparation

The Aushon 2470 Arrayer has a general software program to manage the printing process. The program enables customization of array printing, with parameters such as top and left offset of printing, depositions/feature, slide lot number, number of replicates, dwell time for pins, total number of immersions, maximum number of extractions and wash sequences.

9.2.10.3. Calibration of Values

Each array contains a printed calibrator(s), a series of cell lystates derived from cells treated with a variety of mitogens such that broad pathway activation has been achieved. The calibrator(s) will consist of 6 – 10 dilutions of whole cell lysates from stimulated and unstimulated cells (eg. HeLa cells treated and untreated with pervandate for 30 minutes; jurkat cells treated and untreated with calyculin for 30 minutes; A431 cells treated and untreated with EGF for 30 minutes) pre-mixed in various ratios such that the total protein in any spot does not change, but the phospho-analyte changes in a predictable and defined concentration. Another type of calibrator can be prepared by spiking-in known amounts of recombinant protein or peptides that correspond to the target analyte and react specifically with antibodies directed to the target protein into a lystate that does not contain the target analyte. We print the EXACT SAME CALIBRATOR ON EVERY SINGLE SLIDE. The defining characteristic of this calibrator is that protein concentration does not vary but staining intensity does. Much like a clinical assay run in a diagnostic laboratory, each experimental value is extrapolated to a non-parametric curve fit of the calibrator within he region that span the dynamic range of the population such that results can be compared over time and across arrays. The calibrator is defined either in absolute amounts (if the analyte concentration is known), or in relative units (RUs) if the absolute amount of the analyte within the calibrator is not known. Most applications will use RU calibration units.

9.2.10.4. Data Normalization

Each protein analyte value is normalized to the total amount of protein printed on that spot by first incubated the slide with a florescent stain (Sypro Ruby Blot Stain, Molecular Probes, Eugene OR) that binds to proteins without bias and does not interfere with subsequent antibody binding. The protein loading value is also obtained by a calibrated assay technique. ON EVERY SLIDE WE PRINT A PROTIEN CALIBRATION CURVE OF THE EXACT SAME SAMPLE ON EVERY SINGLE SLIDE. This total protein calibrator consists of a protein lysate, which upon dilution, spans the linear dynamic range of protein concentration. Each sample value is then extrapolated to the calibrator. Consequently, while the total amount of protein may vary in any given sample compared to each other- thus affecting phopsho-protein measurements for each sample, this variance is greatly minimized by such a normalization procedure.

9.2.10.5. Blocking Procedure

Once arrays have been printed and stained for total protein, slides undergo a blocking procedure. Casein based solutions provide a uniform protein solution capable of binding to non antigenic sites on nylon, PVDF and nitrocellulose membranes. Casein blocks these sites,

inhibiting binding of antibody. This results in reduced background staining for reverse phase protein arrays.

9.2.10.6. Staining and Image Acquisition

Arrays are probed using an antibody specific for the phospho-protein, or any protein analyte. Our current repertoire consists of over 350 phopshoproteins that have been extensively pre-validated for specificity using Western blotting and peptide competition. A Dako Cytomation Autostainer (FDA approved for the HercepTest) is used to perform the staining procedure. This includes the processes of incubation with primary antibody, specific for the analyte of interest as well as incubation with secondary antibody. A signal is generated using a near-IR fluorescent dye (LICOR Biosciences) that is coupled to the secondary antibody. The current iteration of the RPPA uses a fluorometric image capture processing system (e.g. NovaRay, Alpha Innotech) for image acquisition. The system measures the sample's fluorescence intensity value, subtracts the background, normalizes the result to the total protein, and extrapolates the value to the non-parametrically fit calibration curve to generate a final intensity value. The median of the triplicate values is reported.

9.2.10.7. Correlation of Calibrated Values with Clinical Outcomes

Final calibrated values of patient samples are then correlated with outcomes results (discontinuous variables (alive v dead, long v short survival), or continuous variables (overall survival, disease free survival, time to progression, etc). These values are usually reported in days, weeks or months. Statistical analysis is used for the correlative findings. Parametric (e.g, Student t-test) or non-parametric (e.g. Wilcoxon Rank Sum) of mean comparison is used, Kaplan Meir and ROC curves are used to uncover relationships between continuous clinical variables and continuous calibrated values. Optimally, any optimal cutpoint found by such analysis should be tested in independent study sets using ROC and or KM type analysis.

9.2.11. *Ex Vivo* Models

9.2.11.1. Organoids

Organoid models will be generated at Thomas Jefferson University using the method previously described by Huch et al. and Boj et al[87, 88]. Our gastroenterologists, via endoscopic ultrasound, will obtain de-identified core biopsy samples of metastatic pancreas tumor. Tumor tissue will be minced and digested with collagenase II in culture media at 37°C for 16 hours. Culture media will be composed of AdDMEM, F12 supplemented with HEPES, Glutamax, penicillin/streptomycin, B27, Primocin, N-acetyl-L-cysteine, RSPO1-conditioned medium, Noggin, EGF, Gastrin, FGF, Nicotinamide, and A83-01. The tissue will be further digested with TrypLE at 37°C for 15 min. It will then be embedded in GFR Matrigel and cultured in culture media versus various treatment conditions. Organoids will be grown in Matrigel for up to one week and then subject to genomic and proteomic evaluation to assess response to treatment.

9.2.11.1.1. Detailed Methodology

Organoid models will be generated at Thomas Jefferson University using the method previously described by Boj et al and Huch et al. [87, 88] One core of tumor tissue will be minced and digested with collagenase II in culture media at 37°C for 16 hours. Culture media will be composed of AdDMEM, F12 supplemented with HEPES, Glutamax, penicillin/streptomycin, B27, Primocin, N-acetyl-L-cysteine, RSPO1-conditioned medium, Noggin, EGF, Gastrin, FGF, Nicotinamide, and A83-01. The tissue will be further digested with TrypLE at 37°C for 15 min. It will then be embedded in GFR Matrigel and cultured in culture media versus various treatment conditions.

Organoids will be grown in Matrigel for up to one week and then subject to genomic and proteomic evaluation to assess response to treatment.

9.2.11.1.2. Shipping Details

Biopsy samples collected for organoids will be collected in pre-supplied Eppendorf tubes containing CRC media and y-compound, and shipped overnight on ice to:

Dr. Jonathan Brody and Joe Cozzitorto
Curtis 618
1015 Walnut Street
Philadelphia, PA 19106

9.2.11.2. Zebrafish Ex-vivo Avatars

9.2.11.2.1. Introduction

Testing of therapeutic agents in patient-derived primary (or metastatic) tumor xenografts (PDX) in nude mice is generally considered the most reliable and convincing demonstration of drug efficacy in pre-clinical models. Advantages include the high efficiency of tumor take and the remarkable genotypic and phenotypic resemblance to the tumor from which the xenograft was derived. However, disadvantages, which include the necessity for large amounts of tissue, expense and the length of time required to carry out the analyses prohibit PDX in mice as a viable method for large-scale drug testing in a personalized medicine setting. Data from Georgetown and other institutions have shown that zebrafish embryos and even adult immuno-compromised zebrafish are excellent hosts for xenografts derived from cultured human tumor cells and are also well suited for drug screening. Our preliminary studies used fresh and cryopreserved pancreatic tumor tissue isolated from seven patients to show that it is possible to simultaneously prepare tumor tissue for zebrafish xenografts (Zevatars), conditional immortalization as well as for collection of pancreatic stellate cells (PSCs) (Table 11). Creation of CRCs and Zevatars was successful in every case and PSCs have been isolated from the earlier collections-we are awaiting results for those patients collected more recently as PSCs take longer to establish. The PSCs we have characterized express cadherin-11, a marker for activated PSCs. In this protocol, we will use the zebrafish embryo as a host for xenografts of cryopreserved fragments of tumor tissue obtained directly from patient biopsies. Preliminary work shows that hundreds, and potentially thousands of embryos bearing living xenografts can be prepared from a single cryopreserved patient specimen in a few hours. As a likely, though not yet defined aim of this protocol, the large number of replicates should allow for testing of many drugs in a PDX setting in a few days.

ID	Date	CRC Fresh	CRC Cryo	Zevatar fresh (n)	Zevatar Cryo (n)	PSC
1A1340	2/27/15	Established	No, all went for Zevatars	Yes (9) other pieces too large	Yes (80)	Yes
1A1386	5/8/15	In culture	Yes	Yes (41)	TBD	No
1A1390	5/15/15	Established	Yes	Yes (41)	TBD	Yes but contaminated
1A1395	5/21/15	In culture	Yes	Yes (74)	TBD	Unknown
1A1399	5/22/15	Established	Yes	Yes (76)	TBD	Yes
1A1400	5/26/15	In culture	Yes	Yes (26)	TBD	Unknown
1A1408	6/4/15	In culture	Yes	ND	TBD	Yes

Table 11. Outcome from 7/10 PDAC specimens collected by Indivumed-Georgetown (February-June 2015). Three additional specimens have been approved for collection by our Biospecimen Use Committee but have yet to be processed. Some CRCs have grown sufficiently that we have cryopreserved a large number of cells (established). Others are still being expanded in culture. Up to 80 Zevatars were prepared but with assistance it is quite likely that several hundred replicates can be obtained from a single patient specimen. ND-not done: TBD to be determined

9.2.11.2.2. Detailed Methodology

Importantly, the zebrafish xenograft studies only need a small amount of tissue. The patient tissue will be processed as soon as it arrives in the core lab and minced into 1-3 mm cubes. To perform patient derived zevatar experiments, zebrafish embryos will injected with small tissue fragments 48 hours post fertilization of the zebrafish. The tissue will be further fragmented with forceps or digested briefly with collagenase to partially dissociate the cellular components. For visualization of the implanted samples, the cells will be labeled with CM-dil CellTracker fluorescent probes from Invitrogen and implanted into zebrafish embryos. Sample implantation and metastases will be monitored by fluorescence microscopy. Imaging will occur within 12 hours following implantation in order to capture initial conditions. At this time, embryos that are not successfully implanted will be removed from the study. The embryos will be imaged again at 2 days post-implantation. Imaging will be performed on an Olympus IX-71 inverted microscope with a color CCD camera. The images will be processed using Image J.

Following tumor implantation, the embryos will be arrayed into 96-well plates where each embryo containing an implant will be imaged. We will capture a bright-field or phase image as well as green fluorescent and red fluorescent images. The red fluorescent image will show the labeled tumor implant. The green fluorescent image shows the vasculature since we will use kdrl:GFP transgenic embryos. This enables more accurate localization of the implant and any movement of tumor cells within the embryo. Finally, the bright-field/phase image ensures we have captured the correct focal plane and enhances our ability to evaluate the health and orientation of the embryos.

The viability of the tumor cells following preparation and labeling as well as post implantation will be determined by fixing and embedding tumor fragments and embryos for histopathology and immunohistochemical analysis. The embryos will be fixed in 4% paraformaldehyde overnight, washed, dehydrated to 70% ethanol, and then taken to HTSR for embedding and sectioning. At this point they can be treated like any other histopathology specimen. Success rates for implanted versus injected cells will be evaluated in terms of cellular behaviors and the viability of the implanted or injected cells. Further, we will identify the cell types in the implanted tumors, as well as those that survive, grow and migrate within the embryo. Unlike mouse xenografts or cultured cells, zebrafish xenograft assays directly measure the behavior of the

implanted cells in real time. In the case of tumor xenografts, multiple cell types along with stroma are present, including components of the immune system. Thus, it is important have an understanding of what cells are being implanted and which cells are surviving, growing, migrating and metastasizing in this assay.

9.2.11.2.3. Sample Collection and Shipping Details

The zebrafish xenograft studies only need a small amount of tissue. Therefore, a single biopsy core will placed in a cryovial containing CRC medium. Unused vials will be shipped to a site on ice when a patient is enrolled in the protocol, prior to the biopsy. The patient samples in the cryovial will be placed on WET ice and shipped out immediately by overnight express to:

Dr. Glasgow's lab
Suite 343, Building D
Georgetown University Medical Center
Washington D.C. 20057

10. ETHICAL CONSIDERATIONS AND STUDY MANAGMENT

This study will be conducted in compliance with the protocol, GCP, HIPAA and all applicable regulatory requirements:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial patients are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. For detailed information on Investigator's and Sponsor's obligation see www.fda.gov/oc/gcp/ and www.ich.org/

10.1. Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by their local institution. All investigators will follow the conflict of interest policy of their local institution.

10.2. Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

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

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

10.3. Required Documentation

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

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.4. Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.5. Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11. REFERENCES

1. Division of Cancer Treatment and Diagnosis (DCTD), N.C.I.N., *Investigator's brochure for PANVAC™ - VF (recombinant vaccinia and fowlpox viruses encoding human Carcinoembryonic antigen, MUC-1, B7.1, intercellular adhesion molecule-I, and leukocyte function-associated antigen-3)*. December 2013, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI): Bethesda, Maryland, USA.
2. MedImmune, L., a Wholly Owned Subsidiary of AstraZeneca PLC, *Investigator's Brochure: A Human Immunoglobulin G1 Kappa (IgG1K) Monoclonal Antibody Directed against Programmed Cell Death Ligand 1 (PD-L1).* September 2015., MedImmune, LLC, a Wholly Owned Subsidiary of AstraZeneca PLC: Gaithersburg, MD, USA.
3. Weinberg, B.A., et al., *Maintenance therapy with capecitabine in patients with resected pancreatic adenocarcinoma after adjuvant therapy: a retrospective cohort study.* Gastrointest Cancer Res, 2014. 7(3-4): p. 91-7.
4. Koopman, M., et al., *Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC).* ASCO Meeting Abstracts, 2014. 32(15_suppl): p. 3504.
5. Altwegg, R., et al., *Second-line therapy for gemcitabine-pretreated advanced or metastatic pancreatic cancer.* World journal of gastroenterology : WJG, 2012. 18(12): p. 1357-1364.
6. Simon, R., *Optimal two-stage designs for phase II clinical trials.* Control Clin Trials, 1989. 10(1): p. 1-10.
7. Jochems, C., et al., *Identification and characterization of agonist epitopes of the MUC1-C oncoprotein.* Cancer Immunol Immunother, 2014. 63(2): p. 161-74.
8. Tsang, K.Y., et al., *Generation of human cytotoxic T cells specific for human carcinoembryonic antigen epitopes from patients immunized with recombinant vaccinia-CEA vaccine.* J Natl Cancer Inst, 1995. 87(13): p. 982-90.
9. Tucker, J.A., et al., *Identification and characterization of a cytotoxic T-lymphocyte agonist epitope of brachyury, a transcription factor involved in epithelial to mesenchymal transition and metastasis.* Cancer Immunol Immunother, 2014. 63(12): p. 1307-17.
10. Karyampudi, L., et al., *Identification of a broad coverage HLA-DR degenerate epitope pool derived from carcinoembryonic antigen.* Cancer Immunol Immunother, 2010. 59(1): p. 161-71.
11. Boyerinas, B., et al., *Antibody-Dependent Cellular Cytotoxicity Activity of a Novel Anti-PD-L1 Antibody Avelumab (MSB0010718C) on Human Tumor Cells.* Cancer Immunol Res, 2015. 3(10): p. 1148-57.
12. Idorn, M., et al., *Correlation between frequencies of blood monocytic myeloid-derived suppressor cells, regulatory T cells and negative prognostic markers in patients with castration-resistant metastatic prostate cancer.* Cancer Immunol Immunother, 2014. 63(11): p. 1177-87.
13. Huang, J., et al., *Soluble CD27-pool in humans may contribute to T cell activation and tumor immunity.* J Immunol, 2013. 190(12): p. 6250-8.
14. Klinger, M., et al., *Combining next-generation sequencing and immune assays: a novel method for identification of antigen-specific T cells.* PLoS One, 2013. 8(9): p. e74231.
15. Yong, S. and S. Lau, *Rapid separation of tryptophan, kynurenines, and indoles using reversed-phase high-performance liquid chromatography.* Journal of chromatography, 1979. 175(2): p. 343-346.
16. Ino, K., et al., *Indoleamine 2,3-dioxygenase is a novel prognostic indicator for endometrial cancer.* Br J Cancer, 2006. 95(11): p. 1555-61.
17. Rodriguez, P.C., et al., *Arginase I-producing myeloid-derived suppressor cells in renal cell carcinoma are a subpopulation of activated granulocytes.* Cancer research, 2009. 69(4): p. 1553-1560.
18. Tcherkas, Y.V., L.A. Kartsova, and I.N. Krasnova, *Analysis of amino acids in human serum by isocratic reversed-phase high-performance liquid chromatography with electrochemical detection.* J Chromatogr A, 2001. 913(1-2): p. 303-8.
19. Radwan, N.A. and N.S. Ahmed, *The diagnostic value of arginase-1 immunostaining in differentiating hepatocellular carcinoma from metastatic carcinoma and cholangiocarcinoma as compared to HepPar-1.* Diagnostic pathology, 2012. 7: p. 149.
20. Zhou, J., et al., *Activation of the PTEN/mTOR/STAT3 pathway in breast cancer stem-like cells is required for viability and maintenance.* Proc Natl Acad Sci U S A, 2007. 104(41): p. 16158-63.

21. Wulfkuhle, J.D., et al., *Multiplexed cell signaling analysis of human breast cancer applications for personalized therapy.* J Proteome Res, 2008. 7(4): p. 1508-17.
22. VanMeter, A., et al., *Reverse-phase protein microarrays: application to biomarker discovery and translational medicine.* Expert Rev Mol Diagn, 2007. 7(5): p. 625-33.
23. Silvestri, A., et al., *Protein pathway biomarker analysis of human cancer reveals requirement for upfront cellular-enrichment processing.* Lab Invest, 2010. 90(5): p. 787-96.
24. Pierobon, M., et al., *Multiplexed cell signaling analysis of metastatic and nonmetastatic colorectal cancer reveals COX2-EGFR signaling activation as a potential prognostic pathway biomarker.* Clin Colorectal Cancer, 2009. 8(2): p. 110-7.
25. Petricoin, E.F., 3rd, et al., *Phosphoprotein pathway mapping: Akt/mammalian target of rapamycin activation is negatively associated with childhood rhabdomyosarcoma survival.* Cancer Res, 2007. 67(7): p. 3431-40.
26. Grubb, R.L., et al., *Pathway biomarker profiling of localized and metastatic human prostate cancer reveal metastatic and prognostic signatures.* J Proteome Res, 2009. 8(6): p. 3044-54.
27. Espina, V., et al., *A portrait of tissue phosphoprotein stability in the clinical tissue procurement process.* Mol Cell Proteomics, 2008. 7(10): p. 1998-2018.
28. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA: a cancer journal for clinicians, 2015. 65(1): p. 5-29.
29. Heinemann, V., et al., *FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial.* The Lancet Oncology, 2014. 15(10): p. 1065-1075.
30. Venook, A.P., et al., *CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC).* J Clin Oncol (Meeting Abstracts), 2014. 32(15_suppl): p. LBA3-.
31. Koopman, M., et al. *Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG)*. in *ASCO Annual Meeting Proceedings*. 2013.
32. Conroy, T., et al., *FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.* The New England journal of medicine, 2011. 364(19): p. 1817-1825.
33. Von Hoff, D.D., et al., *Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine.* N Engl J Med, 2013. 369(18): p. 1691-703.
34. Brahmer, J.R., et al., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.* The New England journal of medicine, 2012. 366(26): p. 2455-2465.
35. Fairman, D., et al., *Pharmacokinetics of MEDI4736, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumors.* J Clin Oncol (Meeting Abstracts), 2014. 32(15_suppl): p. 2602-.
36. Lutzky, J., et al., *A phase 1 study of MEDI4736, an anti-PD-L1 antibody, in patients with advanced solid tumors.* J Clin Oncol (Meeting Abstracts), 2014. 32(15_suppl): p. 3001-.
37. Segal, N.H., et al., *Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody.* ASCO Meeting Abstracts, 2014. 32(15_suppl): p. 3002.
38. Tatipalli, M., et al., *Pharmacokinetics and pharmacodynamics of MEDI4736, a fully human anti-programmed death ligand 1 (PD-L1) monoclonal antibody, in combination with tremelimumab in patients with advanced non-small cell lung cancer (NSCLC).* J Clin Oncol (Meeting Abstracts), 2015. 33(15_suppl): p. e14010-.
39. Zielinski, C.C., *A phase I study of MEDI4736, NNT-PD-L1 antibody in patients with advanced solid tumors.* Translational lung cancer research, 2014. 3(6): p. 406-407.
40. Mu, C.Y., et al., *High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation.* Med Oncol, 2011. 28(3): p. 682-8.
41. Krambeck, A.E., et al., *Survivin and b7-h1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2007. 13(6): p. 1749-1756.

42. Thompson, R.H., et al., *Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma.* Cancer, 2005. 104(10): p. 2084-91.
43. Thompson, R.H., et al., *Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up.* Cancer research, 2006. 66(7): p. 3381-3385.
44. Loos, M., et al., *Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer.* Cancer letters, 2008. 268(1): p. 98-109.
45. Nomi, T., et al., *Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2007. 13(7): p. 2151-2157.
46. Wang, L., et al., *Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma.* World journal of surgery, 2010. 34(5): p. 1059-1065.
47. Hamanishi, J., et al., *Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.* Proceedings of the National Academy of Sciences of the United States of America, 2007. 104(9): p. 3360-3365.
48. Andorsky, D.J., et al., *Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2011. 17(13): p. 4232-4244.
49. Brusa, D., et al., *The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia.* Haematologica, 2013. 98(6): p. 953-963.
50. Keir, M.E., et al., *PD-1 and its ligands in tolerance and immunity.* Annual review of immunology, 2008. 26: p. 677-704.
51. Park, J.-J.J., et al., *B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance.* Blood, 2010. 116(8): p. 1291-1298.
52. Zou, W. and L. Chen, *Inhibitory B7-family molecules in the tumour microenvironment.* Nature reviews. Immunology, 2008. 8(6): p. 467-477.
53. Nordic, B., *INVESTIGATOR'S BROCHURE: CV301 (MVA-BN-CV301 and FPV-CV301) Bavarian Nordic, Version 4.0 Dated 12 Feb 2019.* 2019.
54. Garnett, C.T., et al., *TRICOM vector based cancer vaccines.* Current pharmaceutical design, 2006. 12(3): p. 351-361.
55. Finn, O.J., et al., *MUC-1 epithelial tumor mucin-based immunity and cancer vaccines.* Immunol Rev, 1995. 145: p. 61-89.
56. Tsang, K.Y., et al., *Analyses of recombinant vaccinia and fowlpox vaccine vectors expressing transgenes for two human tumor antigens and three human costimulatory molecules.* Clin Cancer Res, 2005. 11(4): p. 1597-607.
57. Kaufman, H.L., et al., *Poxvirus-based vaccine therapy for patients with advanced pancreatic cancer.* Journal of translational medicine, 2007. 5: p. 60.
58. Morse, M.A., et al., *A randomized phase II study of immunization with dendritic cells modified with poxvectors encoding CEA and MUC1 compared with the same poxvectors plus GM-CSF for resected metastatic colorectal cancer.* Annals of surgery, 2013. 258(6): p. 879-886.
59. PRNewswire. *Therion Reports Results of Phase 3 PANVAC-VF Trial.* [Website] 2006 December 1, 2015]; Available from: http://www.prnewswire.com/news-releases/therion-reports-results-of-phase-3-panvac-vf-trial-and-announces-plans-for-company-sale-56997582.html.
60. Jochems, C., et al., *A combination trial of vaccine plus ipilimumab in metastatic castration-resistant prostate cancer patients: immune correlates.* Cancer immunology, immunotherapy : CII, 2014. 63(4): p. 407-418.
61. Bendell, J.C., et al., *Safety and efficacy of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) and/or FOLFOX in patients (pts) with metastatic colorectal cancer (mCRC).* ASCO Meeting Abstracts, 2015. 33(3_suppl): p. 704.
62. Amatori, F., et al., *Thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase expression in colorectal cancer and normal mucosa in patients.* Pharmacogenet Genomics, 2006. 16(11): p. 809-16.
63. Apetoh, L., et al., *Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy.* Nat Med, 2007. 13(9): p. 1050-9.

64. Hannani, D., et al., *Prerequisites for the antitumor vaccine-like effect of chemotherapy and radiotherapy.* Cancer J, 2011. 17(5): p. 351-8.
65. Akina, T., et al., *The controversial role of ABC transporters in clinical oncology.* Essays in biochemistry, 2011. 50(1): p. 209-232.
66. Zitvogel, L., et al., *The anticancer immune response: indispensable for therapeutic success?* J Clin Invest, 2008. 118(6): p. 1991-2001.
67. Zitvogel, L., O. Kepp, and G. Kroemer, *Decoding cell death signals in inflammation and immunity.* Cell, 2010. 140(6): p. 798-804.
68. Hodge, J.W., et al., *Chemotherapy-induced immunogenic modulation of tumor cells enhances killing by cytotoxic T lymphocytes and is distinct from immunogenic cell death.* Int J Cancer, 2013. 133(3): p. 624-36.
69. Hodge, J.W., et al., *Attacking malignant cells that survive therapy: Exploiting immunogenic modulation.* Oncoimmunology, 2013. 2(12): p. e26937.
70. Fu, T., Y. Shen, and S. Fujimoto, *Tumor-specific CD4(+) suppressor T-cell clone capable of inhibiting rejection of syngeneic sarcoma in A/J mice.* Int J Cancer, 2000. 87(5): p. 680-7.
71. Ghiringhelli, F., et al., *CD4+CD25+ regulatory T cells suppress tumor immunity but are sensitive to cyclophosphamide which allows immunotherapy of established tumors to be curative.* Eur J Immunol, 2004. 34(2): p. 336-44.
72. Muller, A.J. and G.C. Prendergast, *Indoleamine 2,3-dioxygenase in immune suppression and cancer.* Curr Cancer Drug Targets, 2007. 7(1): p. 31-40.
73. Piccirillo, C.A. and E.M. Shevach, *Cutting edge: control of CD8+ T cell activation by CD4+CD25+ immunoregulatory cells.* J Immunol, 2001. 167(3): p. 1137-40.
74. Teicher, B.A., *Transforming growth factor-beta and the immune response to malignant disease.* Clin Cancer Res, 2007. 13(21): p. 6247-51.
75. Woo, E.Y., et al., *Cutting edge: Regulatory T cells from lung cancer patients directly inhibit autologous T cell proliferation.* J Immunol, 2002. 168(9): p. 4272-6.
76. Hodi, F.S., et al., *Improved survival with ipilimumab in patients with metastatic melanoma.* N Engl J Med, 2010. 363(8): p. 711-23.
77. Huang, Y., et al., *Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy.* Proc Natl Acad Sci U S A, 2012. 109(43): p. 17561-6.
78. Liu, C., et al., *BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice.* Clin Cancer Res, 2013. 19(2): p. 393-403.
79. Alfaro, C., et al., *Influence of bevacizumab, sunitinib and sorafenib as single agents or in combination on the inhibitory effects of VEGF on human dendritic cell differentiation from monocytes.* Br J Cancer, 2009. 100(7): p. 1111-9.
80. Roncucci, L., et al., *Aberrant crypt foci in colorectal carcinogenesis. Cell and crypt dynamics.* Cell Prolif, 2000. 33(1): p. 1-18.
81. Pedroni, M., et al., *Microsatellite instability and mismatch-repair protein expression in hereditary and sporadic colorectal carcinogenesis.* Cancer Res, 2001. 61(3): p. 896-9.
82. Zhang, S., et al., *Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults.* J Clin Pharmacol, 2012. 52(1): p. 18-28.
83. Wang, D.D., et al., *Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials.* J Clin Pharmacol, 2009. 49(9): p. 1012-24.
84. Ng, C.M., et al., *Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis.* Pharm Res, 2006. 23(6): p. 1275-84.
85. Narwal, R., L.K. Roskos, and G.J. Robbie, *Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus*, in *Clin Pharmacokinet*. 2013: New Zealand. p. 1017-27.
86. Farsaci, B., et al., *Identification by digital immunohistochemistry of intratumoral changes of immune infiltrates after vaccine in the absence of modifications of PBMC immune cell subsets.* International journal of cancer. Journal international du cancer, 2014. 135(4): p. 862-870.
87. Boj, S.F., et al., *Organoid models of human and mouse ductal pancreatic cancer.* Cell, 2015. 160(1-2): p. 324-38.

88. Huch, M., et al., *In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration.* Nature, 2013. 494(7436): p. 247-50.
88. Kantoff P, Schuetz T, Blumenstein B, Glode L, Bilhartz D, Wyand M, Manson K, Panicali DL, Laus R, Schlom J, Dahut W, Arlen P, Gulley J and Godfrey W (2010a) Overall survival analysis of a Phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol 28(7):1099-1105.
89. Kantoff P, Higano C, Shore N, Berger E, Small E, Penson D, Redfern C, Ferrari A, Dreicer R, Sims R, Xu Y, Frohlich M, Schellhammer P and IMPACT Study Investigators (2010b) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363(5):411-422.
90. Madan R, Gulley J, Fojo T and Dahut W (2010) Therapeutic cancer vaccines in prostate cancer: the paradox of improved survival without changes in Time to Progression. Oncologist 15(9):969-975.

12. APPENDICES

APPENDIX A: STUDY ELIGIBILITY CHECKLIST

A Phase II Trial of the PD-L1 Inhibitor, Durvalumab plus CV301 as Maintenance Therapy for Patients with Metastatic Colorectal or Pancreatic Adenocarcinoma

Patient Initials: _____ Study ID: _____

Instructions: This form and all supporting documentation should be completed by the research staff and faxed to the Lombardi QAO at 202-687-9361 or scanned/emailed to lcccqao@georgetown.edu.

☐Georgetown University Medical Center ☐Emory University ☐Mayo Clinic ☐ MD Anderson

☐ Other: _____

KEY INCLUSION CRITERIA (ALL ITEMS MUST BE CHECKED YES)

YES | NO

☐ | ☐ Histologically proven pancreatic adenocarcinoma or colorectal with radiographically measurable disease

☐ | ☐ Actively on first line therapy for metastatic pancreatic or colorectal adenocarcinoma
- A. Stable on, or responding to 1st line therapy for metastatic disease:
- B. Stable or responding disease at least 8 and not more than 16 weeks after initiating 1st line therapy for metastatic disease. Due to the timing of enrollment, patients who have completed a maximum of 16 weeks of 1st line chemotherapy may be enrolled >16 weeks after initiation of 1st line therapy if disease stability/response (without additional intervening therapy) can be documented within 4 weeks prior to first dose of CV301
- C. Prior adjuvant chemotherapy is allowed, as long as a minimum of 3 months (for pancreatic cancer) and 6 months (for colorectal cancer) has passed between the completion of adjuvant therapy and the start of first line therapy

☐ | ☐ Biopsy accessible tumor deposits (as can best be determined by imaging) – A patient's biopsied lesion must be at least 1cm in diameter (in at least one dimension)

☐ | ☐ Age ≥ 18 years

☐ | ☐ ECOG performance status 0 or 1 (see Table 12 below)

☐ | ☐ Blood Pressure <160/100 mmHg

☐ | ☐ Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to initiation of treatment AND confirmed prior to initiation of treatment on Day 1, and/or postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.

☐ | ☐ Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures

☐ | ☐ Patients must have fully recovered from all effects of surgery. Patients must have had at least two weeks after minor surgery and four weeks after major surgery before starting therapy. Minor procedures requiring "Twilight" sedation such as endoscopies, tumor biopsies, or mediport placement may only require a 24-hour waiting period, but this must be discussed with an investigator.

☐ | ☐ Life expectancy > 12 weeks

CRITICAL LAB VALUES (ALL MUST BE CHECKED YES)

YES | NO

☐ | ☐ Absolute neutrophil count (ANC) ≥ 1,500/mm^3

☐ | ☐ Platelets ≥ 100,000/mm^3

☐ | ☐ Hemoglobin ≥ 9.0 g/dL

☐ | ☐ Serum creatinine ≤ 1.5 X the upper limit of normal of the institution's normal range OR creatinine clearance ≥ 40 mL/min/1.73 m^2 for subjects with creatinine level above the upper limit of normal

☐ | ☐ AST, ALT, and alkaline phosphatase ≤ 2.5 X the upper limit of normal of the institution's normal range. For patients with known hepatic metastases, AST and ALT ≤ 5 X the upper normal limit of institution's normal range

☐ | ☐ Bilirubin ≤ 1.5 X the upper limit of normal of the institution's normal range

☐ | ☐ Prothrombin Time and Partial Thromboplastin Time (PTT) ≤ 1.5 X the upper limit of the institution's normal range

☐ | ☐ INR (International Normalized Ratio) < 1.5, subjects on anticoagulation will be permitted as long as the INR is in an acceptable therapeutic range as determined by the investigator

CRITICAL EXCLUSION CRITERIA (ELIGIBLE PATIENTS MUST ALL BE CHECKED NO)

☐ | ☐ Prior vaccine or immunotherapy OR prior solid organ transplant

☐ | ☐ History of autoimmune disease or prior bone marrow transplant OR treatment with immunosuppressive medications

☐ | ☐ History of pulmonary fibrosis OR inflammatory bowel disease

☐ | ☐ Positive test for HIV; or active hepatitis B or C, or tuberculosis

☐ | ☐ Recent severe infections, or actively on antibiotics

☐ | ☐ Live, attenuated vaccine within 4 weeks

☐ | ☐ Allergic/hypersensitivity reaction to antibodies

☐ | ☐ Anti-cancer therapy within 2 weeks

☐ | ☐ The subject has had another active malignancy within the past five years except for cervical cancer in situ, in situ carcinoma of the bladder or non-melanoma carcinoma of the skin. Questions regarding the inclusion of individual subjects should be directed to the Study Chair

☐ | ☐ CNS Metastases (if yes, see details in inclusion/exclusion)

☐ | ☐ QTc ≥470ms on EKG

☐ | ☐ Grade ≥2 proteinuria

☐ | ☐ Patient is receiving any other investigational agents

☐ | ☐ Cardiovascular disease problems including unstable angina, therapy for life-threatening ventricular arrhythmia, or myocardial infarction, stroke, or congestive heart failure within the last 6 months

☐ | ☐ Life-threatening visceral disease or other severe concurrent disease

☐ | ☐ Woman who is pregnant or breast feeding

☐ | ☐ Subjects with uncontrolled seizures

☐ | ☐ History of allergic reactions attributed to compounds of similar chemical or biologic composition to durvalumab or any excipient or any egg products

☐ | ☐ Anticipated survival under 2months

☐ | ☐ Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

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

Table 12: ECOG Performance Status Scale (Repeated)

APPENDIX B: PATIENT REGISTRATION FORM

A Phase II Trial of the PD-L1 Inhibitor, Durvalumab plus CV301 as Maintenance Therapy for Patients with Metastatic Colorectal or Pancreatic Adenocarcinoma

Patient Initials: _____ Study ID (IRB#): _____

Instructions: This form and all supporting documentation should be completed by the research staff and faxed to the Lombardi QAO at 202-687-9361 or scanned/emailed to lcccqao@georgetown.edu.

Enrolling site:

□ Georgetown University Medical Center □ Emory University □ Mayo Clinic □ MD Anderson
□ Other:_____

1. Site PI: _____
2. Enrolling MD: _____
3. Date Informed Consent signed: ___/___/_____
4. Date HIPAA authorization signed: ___/___/_____
5. Proposed Start date for Treatment: ___/____/_____
6. Treatment Location: _____
7. Date of last chemotherapy: ___/____/_____
8. Prior antineoplastic therapy- ie. Cytotoxic, Cytokine base immunotherapy, immunoregulatory antibody therapy, radiation (Date/Type):

_____

_____

_____

9. Please fax documentation supporting eligibility per protocol (Check those included):

□ Pathology Report
□ Physicians Note validating:
  ▪Previous treatments
□ CT showing RECIST 1.1 criteria
□ Laboratory Results
□ Past Medical History

ON-STUDY CARD

STUDY NUMBER:_____
DOB: ____/_____/_____
Zip Code: _____
Race: □ African American
□ Asian
□ Caucasian
□ Hispanic
□ Native American
□ Pacific Islander
□ Other
□ Unknown

Gender: □ Male □ Female □ Unknown
Treating Physician: _____
RN: _____

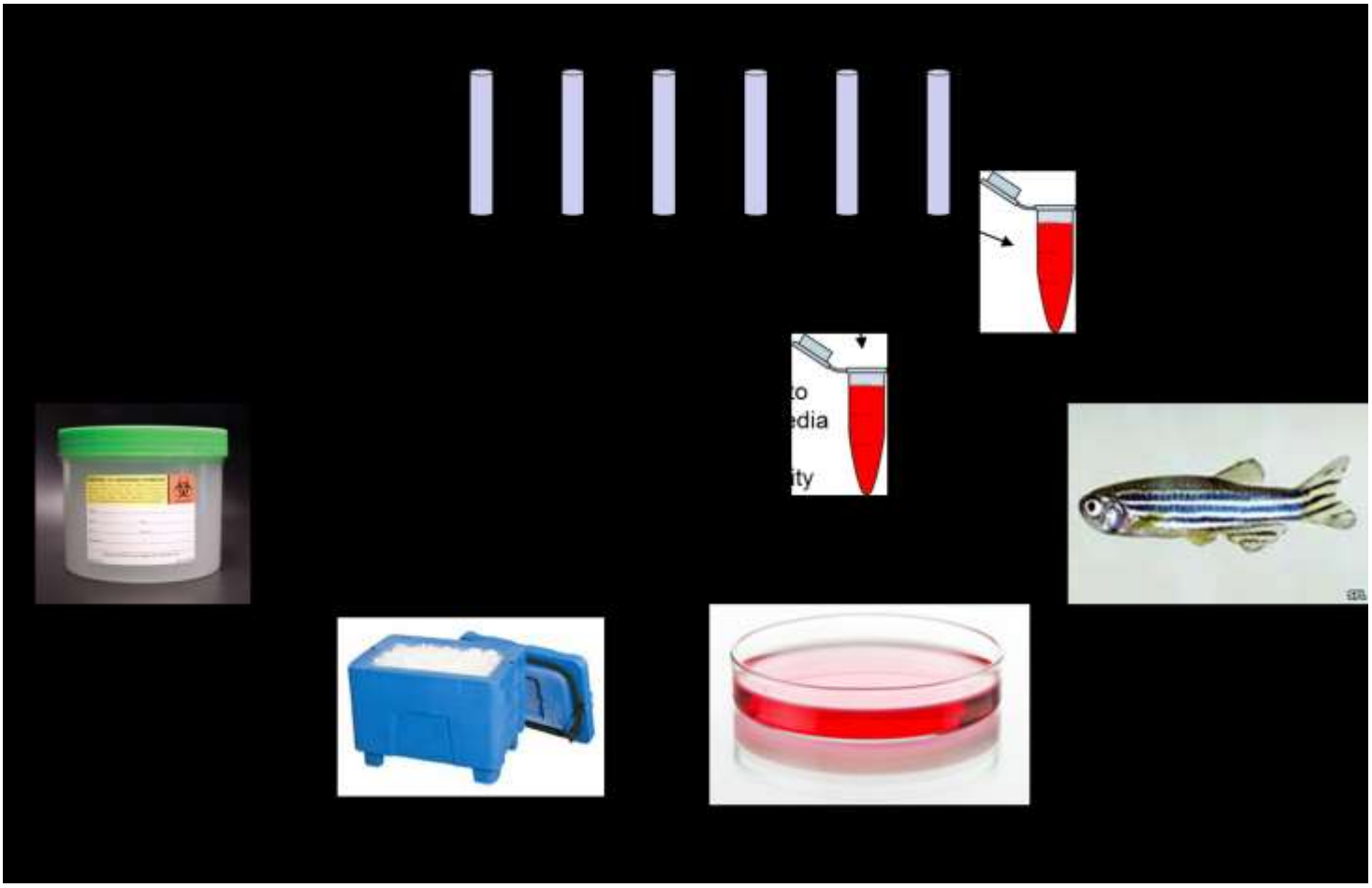
Ethnicity: □ Hispanic or Latino
□ Not Hispanic or Latino
□ Unknown
Consent Approval Date: ___/____/_____
Screen Failure: □ Yes □ No
Baseline Start Date: ____/____/_____
On Study Date: ____/____/_____

Protocol Waiver: □ Yes □ No
Reason: _____
Registration Site: _____
First Scheduled Date: ____/____/_____
Primary Site:_____

FOR QAO USE ONLY:
Subject Study ID: _____
Comments:

APPENDIX C SAMPLE COLLECTION AND SHIPPING INFORMATION

Tissue Prioritization Schema



Instructions for Collection and Shipping of Research Samples

Please note: for all shipping, a Georgetown FedEx Account Number will be supplied

1) Labeling of Blood Samples

Research specimens will be de-identified and labeled with a 14 character study label (AA-X-XX-XX-X-MM/DD/YY):

- The first two characters will be the patient's initials
- The third character will be the site number from which the patient was enrolled (single digit)
  - 1 = Georgetown
  - 2 = Mayo Clinic
  - 3 = Emory University
- The fourth and fifth characters will be the patient study number (e.g. 01, 02, 03, etc.)
- The sixth and seventh characters will be the correlative technique (two digit)
  - 01 = NIH Formalin
  - 02 = George Mason RPPA
  - 03 = NIH Frozen
  - 04 = TJU Organoids
  - 05 = Lombardi Zebrafish
  - 06= Blood collection: Serum and PBMC
  - Additional numbers can be added as needed for future research samples
- The eighth character will be the timing of collection
  - 1 = Pre-treatment biopsy/sample

- 2 = On treatment biopsy/sample
- 3 = Serum collection

o The final characters will be the date in MM/DD/YY format

Example: AA-1-01–01-1-10/14/18
Protocol: 2017-1189

2) Tumor Biopsy Samples

a) Supplies

For the trial, the individual sites will supply the following:

- Wet and dry ice (typically available on site)
- Green top (Na heparin, 10 mL) tubes
- Red serum separator (8 mL) tubes

Additionally, the site will order the following supplies directly from VWR:

Item	Details	Catalog #	Price
EHS Combo Shipping System	Case of 2	10029-406	$53.34
Cat B Ambient 95kPa Bag, 6-Tube	Case of 16	10029-264	$66.20
Corning Cryovial tube Round-Bottom (2mL) , Self-Standing	Case of 500	66021-974	$372.39
Prefilled 10% Neutral Buffered Formalin	Case of 48 (40ml)	16004-115	$74.70
Disposable forceps 121 mm ($4^{3}/_{4}$")	Pack of 100	12576-934	$200.42

Finally, the following materials will need to be sent to the participating sites upon request and stored. The first batch will be shipped upon request once a patient has been consented.

i) Organoid Media
- Biopsy samples collected for organoids will be collected in pre-supplied Eppendorf tubes containing Advanced DMEM/F12 (5mL) with Glutamax 1%, Pen/Strep 1%, and HEPES Buffer 1%. Media will be sent to the sites in batches of 5 upon request from Dr. Brody's lab.
- To be sent to the sites in batches of 5
- Sent to the sites upon request from Dr. Brody's lab
- Please contact Dr. Brody for a shipment - jonathan.brody@jefferson.edu
- Store at 4°C
- Each batch expires after 1 month

ii) Zebrafish (CRC) Media
- Biopsy samples will placed in a cryovial containing CRC medium + y-compound
- Vials will be shipped to the sites in batches of 5, upon request from Dr. Glasgow's Lab
- Please contact Shaila Mudambi for a shipment - sm3468@georgetown.edu
- Store at 4°C
- Each batch expires after 1 month

b) Collection Details (Tumor samples)

i) Formalin samples (First two cores)
- The first two cores (Correlative sample and phosphoprotein sample) should be placed INDIVIDUALLY in a single standard formalin vials and submitted to histopathology for paraffin embedding
- The samples do NOT require surgical pathology assessment.
- The samples from these FFPE blocks should not be cut for an H&E analysis.

ii) Frozen Samples (Third and fourth core)
- The next two cores should be placed INDIVIDUALLY in a single cryovials and snap frozen in liquid nitrogen, and stored at -80oC.

iii) Organoid Samples (Fifth core)
- The fifth core (organoid sample) will be collected in pre-supplied Eppendorf tubes containing Advanced DMEM/F12 (5mL) with Glutamax 1%, Pen/Strep 1%, and HEPES Buffer 1%.

iv) Zebrafish Samples (Sixth core)
- The sixth core will be placed in a pre-provided Eppendorf tubes with CRC media with y-compound.

c) Shipping Details (Tumor samples)

i) Formalin samples (First core)
- FFPEs of the first cores (Correlative sample) can be sent in protective wrapping in batches to:

  Leidos
  Biomedical Research
  Attn: Bill Kopp/Theresa Burks
  1050 Boyles Street
  Bldg. 469/Room 121
  Frederick, MD 21702
  Phone 301-846-5125, or 301-846-1707
- Please notify the Frederick laboratory when specimens are being shipped. Please email Frederick prior to shipping to notify the lab.
- Emails should be sent to the following individuals:

  Bill Kopp, koppw@mail.nih.gov
  Theresa Burks, burkst@mail.nih.gov
  Caroline Jochems, jochemscm@mail.nih.gov
  Michael Pishvaian, pishvaim@georgetown.edu
- Additionally, NO specimens should be shipped on Fridays or the day before a Federal holiday.

ii) Formalin samples (Second core)
- FFPEs of the second cores (Phosphoprotein sample) can be sent in protective wrapping in batches to:

  Emanuel F Petricoin, PhD
  University Professor
  Co-Director Center for Applied Proteomics and Molecular Medicine
  School of Systems Biology
  George Mason University
  10920 George Mason Circle
  Room 2006 Institute of Advanced Biomedical Research
  Manassas, VA 20110
- Please notify Dr. Petricoin's laboratory when specimens are being shipped. Please email Dr. Petricoin prior to shipping to notify the lab.
- Emails should be sent to the following individuals:

  Chip Petricoin epetrico@gmu.edu
- Additionally, NO specimens should be shipped on Fridays or the day before a Federal holiday.

iii) Frozen cores can be sent by overnight shipping ON DRY ICE in batches to:
- Please notify the Frederick laboratory when specimens are being shipped. Please email Frederick prior to shipping to notify the lab.
- Emails should be sent to the following individuals:

  Bill Kopp, koppw@mail.nih.gov
  Theresa Burks, burkst@mail.nih.gov

Caroline Jochems, jochemscm@mail.nih.gov
Michael Pishvaian, pishvaim@georgetown.edu

- Additionally, NO specimens should be shipped on Fridays or the day before a Federal holiday.

iv) Organoid Samples can be sent on WET ICE immediately to:

Dr. Jonathan Brody and Joe Cozzitorto
Immediate attention
Curtis 618
1015 Walnut Street
Philadelphia, PA 19106

- Please notify Dr. Brody when specimens are being shipped. Please email Dr. Brody prior to shipping to notify the lab.
- Emails should be sent to the following individuals:

Jonathan Brody jonathan.brody@jefferson.edu
Henry Thomsett henry.thomsett@jefferson.edu
Monique Maubert monique.maubert@jefferson.edu

- Additionally, NO specimens should be shipped on Fridays or the day before a Federal holiday.

v) Zebrafish Samples can be sent on WET ICE immediately to:

Dr. Glasgow's lab
Suite 343, Building D
Georgetown University Medical Center
Washington D.C. 20057

- Please notify Dr. Glasgow when specimens are being shipped. Please email Dr. Glasgow prior to shipping to notify the lab.
- Emails should be sent to the following individuals:

Eric Glasgow eg239@georgetown.edu
Shaila Mudambi sm3468@georgetown.edu
Steve Byers byerss@georgetown.edu
Michael Pishvaian pishvaim@georgetown.edu

- Additionally, NO specimens should be shipped on Fridays or the day before a Federal holiday.

d) Blood Samples

i. Collection:
   - 6 green top (Na heparin, 10 mL) tubes
   - 2 red serum separator (8 mL) tubes

ii. Timing - Blood is collected at the following timepoints:
   - On the first treatment day (Week 1, CV301 alone)
   - Week 9
   - Week 17
   - Week 49
   - At the off study visit

iii. Shipping:

- **Blood samples are to be sent on the day of draw by overnight shipping (ambient temperature) to:**

  Leidos
  Biomedical Research
  Attn: Bill Kopp/Theresa Burks
  1050 Boyles Street
  Bldg. 469/Room 121
  Frederick, MD 21702
  Phone 301-846-5125, or 301-846-1707

- Please notify the Frederick laboratory when specimens are being shipped. Please email Frederick prior to shipping to notify the lab.
- Emails should be sent to the following individuals:

  Bill Kopp, koppw@mail.nih.gov
  Theresa Burks, burkst@mail.nih.gov
  Caroline Jochems, jochemscm@mail.nih.gov
  Michael Pishvaian, pishvaim@georgetown.edu

- Additionally, NO specimens should be shipped on Fridays or the day before a Federal holiday.

APPENDIX D FLOW CYTOMETRY ASSAYS

Table 13. Flow Cytometry Markers. Flow cytometry analysis of parental immune cell types in PBMCs using 30 unique markers to identify 123 subsets

1. **CD4$^+$ T cells:** Helper T lymphocytes (32 subsets)
2. **CD8$^+$ T cells:** Cytotoxic T lymphocytes (29 subsets)
   - **Markers of PD-1 pathway and T cell activation (in CD4 and CD8):**
     - **EOMES:** activation
     - **TCR:** activation
     - **Tbet:** activation
     - **BATF:** activation/exhaustion
   - **Maturation status of T cells (in CD4 and CD8):**
     - **Naïve:** CD45RA$^+$ CCR7$^+$
     - **Central Memory (CM):** CD45RA$^-$ CCR7$^+$
     - **Effector Memory (EM):** CD45RA$^-$ CCR7$^-$
     - **Terminal (EMRA):** CD45RA$^+$ CCR7$^-$
   - **T cell markers (in CD4 and CD8):**
     - **CTLA-4:** inhibition
     - **PD-1:** activation/inhibition
     - **PD-L1:** activation/cross-inhibition
     - **TIM-3:** inhibition
     - **ICOS:** activation (only on CD4)
3. **Tregs:** Regulatory T lymphocytes (CD4$^+$ CD25$^+$ FoxP3$^+$ CD127$^-$) (7 subsets)
   - **CD45RA:** Tregs highly expandable *in vitro*
   - **CTLA-4:** Treg suppression
   - **CD49d$^-$:** suppressive Tregs
   - **ICOS:** Treg suppression
   - **PD-1:** activation/inhibition
   - **PD-L1:** cross-inhibition
4. **B cells:** CD19$^+$ (5 subsets)
   - **CTLA-4:** inhibition
   - **TIM-3:** inhibition
   - **PD-1:** activation/inhibition
   - **PD-L1:** cross-inhibition
5. **NK:** Natural killer cells (CD56$^+$ CD3$^-$) (20 subsets)
   - **CD16$^+$ CD56^{dim}:** Mature, lytic
   - **CD16$^+$ CD56^{br}:** Functional intermediate, lytic and cytokine production
   - **CD16$^-$ CD56^{br}:** Immature, cytokine production, abundant in placenta
   - **CD16$^-$ CD56^{dim}:** non-lytic, non-cytokine production
   - **TIM-3:** activation
   - **PD-1:** activation/inhibition
   - **PD-L1:** cross-inhibition
6. **NK-T:** CD56$^+$ CD3$^+$ (4 subsets)
   - **TIM-3:** activation
   - **PD-1:** activation/inhibition
   - **PD-L1:** cross-inhibition
7. **cDCs:** conventional DC (CD3$^-$CD56$^-$CD1c$^+$CD303$^-$) (5 subsets)
8. **pDCs:** plasmacytoid DC (CD3$^-$CD56$^-$CD1c$^-$CD303$^+$) (5 subsets)
   - **Markers of DC activation**
     - **CD83:** activation
     - **TIM-3:** inhibition
     - **PD-1:** activation/inhibition
     - **PD-L1:** cross-inhibition
9. **MDSCs:** Myeloid-derived suppressor cells (CD11b$^+$ HLA-DR$^{low/-}$ CD33$^+$) (16 subsets)
   - **CD14:** Common Myeloid Marker (high in monocytes, dim in granulocytes)
   - **CD15:** Granulocyte marker
   - **CD16:** most immature MDSCs
   - **PD-1:** activation/inhibition
   - **PD-L1:** cross-inhibition

Table 14. Antibodies used for 5 panel stain to identify 123 peripheral immune cell subsets. Panel 1: PD-1 signaling; Panel 2: $CD4^+$ T cells, $CD8^+$ T cells, B cells; Panel 3: Tregs; Panel 4: NK, NK-T, cDC, pDC; Panel 5: MDSC. Intracellular antibodies are underlined, and clones and company are listed under each antibody.

Fluorochrome	Panel 1	Panel 2	Panel 3	Panel 4	Panel 5
FITC	-	CTLA-4 (A3.4H2.H12, LS Bio)	CTLA-4 (A3.4H2.H12, LS Bio)	CD3 (HIT3a, BD)	CD15 (HI98, Ebioscience)
PE	PD-1 (MIH4, BD)	PD-1 (MIH4, BD)	PD-1 (MIH4, BD)	PD-1 (MIH4, BD)	PD-1 (MIH4, BD)
PerCP-Cy5.5	EOMES (WD1928, Ebioscience)	CCR7 (150503, BD)	ICOS (C398.4A, Biolegend)	CD303 (201A, Biolegend)	-
PECy7	PD-L1 (MIH1, BD)	PD-L1 (MIH1, BD)	PD-L1 (MIH1, BD)	PD-L1 (MIH1, BD)	PD-L1 (MIH1, BD)
BV421	TCR (IP26, Biolegend)	Tim-3 (F38-2E2, Biolegend)	FoxP3 (206D, Biolegend)	Tim-3 (F38-2E2, Biolegend)	CD14 (MOP9, BD)
V500	CD4 (OKT4, Biolegend)	CD19 (HIB19, Biolegend)	CD49d (9F10, Biolegend)	CD83 (HB15e, BD)	CD16 (3G8, Biolegend)
BV605	Tbet (4B10, Biolegend)	CD4 (RPA-T4, BD)	CD4 (RPA-T4, BD)	CD56 (HCD56, Biolegend)	HLA DR (L243, Biolegend)
Dapi	Live/Dead (Invitrogen)	Live/Dead (Invitrogen)	Live/Dead (Invitrogen)	Live/Dead (Invitrogen)	Live/Dead (Invitrogen)
APC	BATF (MBM7C7, Ebioscience)	-	CD25 (M-A251, Biolegend)	-	CD33 (WM53, Biolegend)
AF700	-	CD45RA (HI100, BD)	CD45RA (HI100, BD)	CD16 (3G8, Biolegend)	-
APC Cy7	CD8 (RPA-T8, Biolegend)	CD8 (RPA-T8, Biolegend)	CD127 (eBioRDR5, Ebioscience)	CD1c (L161, Biolegend)	CD11b (ICRF44, BD)

Table 15. Complete list of 123 peripheral immune cell subsets analyzed by flow cytometry. Nine standard subsets were identified as well as 114 subsets relating to maturation and function within the standard subsets.

1. Total $CD4^+$ T cells
   - $PD\text{-}L1^+$ CD4
   - $PD\text{-}1^+$ CD4
   - $EOMES^+$ CD4
   - TCR^+ CD4
   - $Tbet^+$ CD4
   - $BATF^+$ CD4
   - $CTLA\text{-}4^+$ CD4
   - $Tim\text{-}3^+$ CD4
   - $ICOS^+$ CD4
     - $PD\text{-}L1^+$ $ICOS^+$ CD4
     - $PD\text{-}1^+$ $ICOS^+$ CD4
   - Total naïve ($CCR7^+CD45RA^+$) CD4
     - $PD\text{-}L1^+$ naïve CD4
     - $PD\text{-}1^+$ naïve CD4
     - $CTLA\text{-}4^+$ naïve CD4
     - $Tim\text{-}3^+$ naïve CD4
   - Total central memory ($CCR7^+$ $CD45RA^-$) CD4
     - $PD\text{-}L1^+$ CM CD4
     - $PD\text{-}1^+$ CM CD4
     - $CTLA\text{-}4^+$ CM CD4
     - $Tim\text{-}3^+$ CM CD4
   - Total effector memory ($CCR7^-$ $CD45RA^-$) CD4
     - $PD\text{-}L1^+$ EM CD4
     - $PD\text{-}1^+$ EM CD4
     - $CTLA\text{-}4^+$ EM CD4
     - $Tim\text{-}3^+$ EM CD4
   - Total EMRA ($CCR7^-CD45RA^+$) CD4
     - $PD\text{-}L1^+$ EMRA CD4
     - $PD\text{-}1^+$ EMRA CD4
     - $CTLA\text{-}4^+$ EMRA CD4
     - $Tim\text{-}3^+$ EMRA CD4
2. Total $CD8^+$ T cells
   - $PD\text{-}L1^+$ CD8
   - $PD\text{-}1^+$ CD8
   - $EOMES^+$ CD8
   - TCR^+ CD8
   - $Tbet^+$ CD8
   - $BATF^+$ CD8
   - $CTLA\text{-}4^+$ CD8
   - $Tim\text{-}3^+$ CD8
   - Total naïve ($CCR7^+CD45RA^+$) CD8
     - $PD\text{-}L1^+$ naïve CD8
     - $PD\text{-}1^+$ naïve CD8
     - $CTLA\text{-}4^+$ naïve CD8
     - $Tim\text{-}3^+$ naïve CD8
   - Total central memory ($CCR7^+CD45RA^-$) CD8
     - $PD\text{-}L1^+$ CM CD8
     - $PD\text{-}1^+$ CM CD8
     - $CTLA\text{-}4^+$ CM CD8
     - $Tim\text{-}3^+$ CM CD8
   - Total effector memory ($CCR7^-$ $CD45RA^-$) CD8
     - $PD\text{-}L1^+$ EM CD8
     - $PD\text{-}1^+$ EM CD8
     - $CTLA\text{-}4^+$ EM CD8
     - $Tim\text{-}3^+$ EM CD8
   - Total EMRA ($CCR7^-CD45RA^+$) CD8
     - $PD\text{-}L1^+$ EMRA CD8
     - $PD\text{-}1^+$ EMRA CD8
     - $CTLA\text{-}4^+$ EMRA CD8
     - $Tim\text{-}3^+$ EMRA CD8
3. Total Tregs
   - $PD\text{-}L1^+$ Tregs
   - $PD\text{-}1^+$ Tregs
   - $CTLA\text{-}4^+$ Tregs
   - $ICOS^+$ Tregs
   - $CD45RA^+$ Tregs
   - $CD49d^-$ Tregs
4. Total B cells
   - $PD\text{-}L1^+$ B cells
   - $PD\text{-}1^+$ B cells
   - $CTLA\text{-}4^+$ B cells
   - $Tim\text{-}3^+$ B cells
5. Total NK
   - $PD\text{-}L1^+$ NK
   - $PD\text{-}1^+$ NK
   - $Tim\text{-}3^+$ NK
   - Total mature ($CD16^+$ $CD56^{dim}$) NK
     - $PD\text{-}L1^+$ mature NK
     - $PD\text{-}1^+$ mature NK
     - $Tim\text{-}3^+$ mature NK
   - Total functional intermediate ($CD16^+$ $CD56^{bx}$) NK
     - $PD\text{-}L1^+$ functional intermediate NK
     - $PD\text{-}1^+$ functional intermediate NK
     - $Tim\text{-}3^+$ functional intermediate NK
   - Total immature ($CD16^-$ $CD56^{bx}$) NK
     - $PD\text{-}L1^+$ immature NK
     - $PD\text{-}1^+$ immature NK
     - $Tim\text{-}3^+$ immature NK
   - Total unconventional ($CD16^-$ $CD56^{dim}$) NK
     - $PD\text{-}L1^+$ unconventional NK
     - $PD\text{-}1^+$ unconventional NK
     - $Tim\text{-}3^+$ unconventional NK
6. Total NK-T
   - $PD\text{-}L1^+$ NK-T
   - $PD\text{-}1^+$ NK-T
   - $Tim\text{-}3^+$ NK-T
7. Total cDC
   - $PD\text{-}L1^+$ cDC
   - $PD\text{-}1^+$ cDC
   - $CD83^+$ cDC
   - $Tim\text{-}3^+$ cDC
8. Total pDC
   - $PD\text{-}L1^+$ pDC
   - $PD\text{-}1^+$ pDC
   - $CD83^+$ pDC
   - $Tim\text{-}3^+$ pDC
9. Total MDSC
   - $PD\text{-}L1^+$ MDSC
   - $PD\text{-}1^+$ MDSC
   - $CD16^+$ MDSC
   - Total monocytic ($CD14^+$ $CD15^-$) MDSC
     - $PD\text{-}L1^+$ mMDSC
     - $PD\text{-}1^+$ mMDSC
     - $CD16^+$ mMDSC
   - Total granulocytic ($CD14^-$ $CD15^+$) MDSC
     - $PD\text{-}L1^+$ gMDSC
     - $PD\text{-}1^+$ gMDSC
     - $CD16^+$ gMDSC
   - Total lineage negative ($CD14^-$ $CD15^-$) MDSC
     - $PD\text{-}L1^+$ lin neg MDSC
     - $PD\text{-}1^+$ lin neg MDSC
     - $CD16^+$ lin neg MDSC

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab

	Immune-Mediated Reactions	
	Dose Modifications	**Toxicity Management**
Immune-related Adverse Events (Overall Manage-ment For toxicities not noted below)	Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of irAEs follow the guidelines presented in this table - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) - In the absence of a clear alternative etiology, all events should be considered potentially immune related. - Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events - For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent - If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper) - More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. - Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient
	Grade 1 No dose modification Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study treatment can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper • Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	
	Grade 3 Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4 Permanently discontinue study drug/study regimen Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Pneumo-nitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	General Guidance	Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment and after completion of steroid taper	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii]1 – Consider pulmonary and infectious disease consult – Consider as necessary discussing with study physician

1 ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Obtain pulmonary and infectious disease consult - Hospitalize the patient - Supportive Care (oxygen, etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii]
Diarrhea/ Entero-colitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance	- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea : - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3/Grade 4 • If toxicity improves to ≤ Grade 1, then study drug/study regimen can be resumed after completion of steroid taper	For Grade 2 diarrhea: - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent - If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			- If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks2). . **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab - Consult study physician if no resolution to ≤ Grade 1 in 3-4 days - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening conse-quences)	Permanently discontinue study drug/study regimen	For Grade 3 or 4 diarrhea: - Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). - Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs) Infliximab should not be used for manageme nt of Immune Related Hepatitis	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin - Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications) For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol

2 ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline, resume study drug/study regimen after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN • Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline within 14 days and after completion of steroid taper Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen Permanently discontinue study drug/study regimen	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause	
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade	General Guidance	– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started.

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			– Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	– Carefully monitor serum creatinine on daily basis – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper	For Grade 2 : – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: - Consult dermatology - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent - Consider hospitalization - Monitor extent of rash [Rule of Nines] - Consider skin biopsy (preferably more than 1) as clinically feasible. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrin-opathy (e.g., hyperthy-roidism, hypothy-roidism, hypopitui-tarism, adrenal insuffi-ciency, etc.)	Any Grade (Depending on the type of endocrino-pathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/se-verity)	General Guidance	- Consult Endocrinologist - Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) - Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. - If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrino-pathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) - Monitor patient with appropriate endocrine function tests - If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent visits as clinically indicated and consider endocrinology consult.

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 2 (Depending on the type of endocrino-pathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event stabilizes after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled ,2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	For Grade 2: (including those with symptomatic endocrinopathy) - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Initiate hormone replacement as needed for management - Evaluate endocrine function, and as clinically indicated, consider pituitary scan - For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). - - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4 (Depending on the type of endocrinopath y, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper	For Grade 3 or 4: - Consult endocrinologist - Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent - Administer hormone replacement therapy as necessary. - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity - Once improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) - Discuss with study physician

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Immune mediated Neurotox-icity (to include but not limited to limbic encepha-litis, autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade	General Guidance	– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See “Any Grade” recommendations above
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1 For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper	– Discuss with the study physician – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3	Hold Study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	For Grade 3 or 4: – Discuss with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG)

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 4	• Permanently discontinue study drug/study regimen	– Once stable, gradually taper steroids over ≥4 weeks
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		General Guidance	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation – Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	– Discuss with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 – Discuss with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy			
	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: - Discuss with study physician - Recommend hospitalization - Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy		
Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	– Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses – Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Appendix E. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy		
Non-immune Mediated Reactions **(Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"**		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

Abbreviations:

AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

---

[i] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

[ii] NCI CTCAE version 4.03

[iii] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

ibFDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation NCI CTCAE version 4.03 iv