Investigational Drug Substance	Durvalumab (MEDI4736) IND 138336
Study Number	ESR 15 11078
Version Number	1.09
Date	**01 Feb 2018**

Phase II trial of in situ tumor vaccination using durvalumab and "booster" radiation therapy in patients with metastatic adenocarcinoma of the pancreas who have progressed through first-line chemotherapy.

Sponsor: **Miami Cancer Institute at Baptist Health, Inc.**

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PROTOCOL SYNOPSIS

Clinical Protocol

Study Title: Phase II trial of in situ tumor vaccination using durvalumab and "booster" radiation therapy in patients with metastatic adenocarcinoma of the pancreas who have progressed through first-line chemotherapy.
Protocol Number: ESR 15 11078
Clinical Phase: II
Study Duration: 4 years
Investigational Products: Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Radiation therapy (RT) will be delivered to 2 radiographically distinct pancreatic cancer lesions with concurrent durvalumab.
Research Hypothesis: The combination of ionizing radiation and immunotherapy (durvalumab) is well tolerated and stimulates a clinically significant pancreas-cancer specific immune response.
Objectives: **Primary Objectives:** The primary objective will be to evaluate whether the combination of RT and durvalumab can improve median PFS compared to chemotherapy historical control data in metastatic pancreas cancer patients who have progressed through first-line chemotherapy. **Secondary Objective(s)**: Secondary endpoints include evaluation of toxicity, overall survival, overall response rate, clinical benefit rate, and time to in-field progression. **Exploratory Objective(s):** Hypothesis-generating post-hoc analysis will be carried out since our study will not be powered to formally test pre-defined subgroup analyses. The following will be explored: 1. Is there any correlation between PD-L1 expression level from the initial biopsy and efficacy of durvalumab with RT? 2. Is there any correlation between durvalumab with RT with levels of CD8 T cells, regulatory T cells, or myeloid derived suppressor cells in the peripheral blood at various intervals before, during, and after therapy? Is there any correlation between changes in levels of these cells over time and efficacy? 3. Is there a correlation between CA19-9 level and progression free survival and radiographic response?

Study Design: Durvalumab every 4 weeks until disease progression or unacceptable toxicity; 3-fraction radiation to one lesion during week 3 and 3-fraction radiation to a second lesion during week 5.
Number of Centers: 1
Number of Subjects: 39
Study Population: Metastatic pancreatic adenocarcinoma patients who have progressed through first-line chemotherapy
Inclusion Criteria: • Age ≥18 years at time of study entry. • Biopsy-proven metastatic pancreatic adenocarcinoma with progression through standard first-line chemotherapy. Chemotherapy given as part of prior chemoradiation does not count as a line of therapy. Chemotherapy given as part of prior chemoradiation in the setting of non-metastatic pancreatic cancer does not count as a line of therapy. • At least 3 radiographically distinct pancreatic cancer lesions that are measurable by RECIST 1.1 criteria, including 2 that are eligible for RT. • Lesions that will receive RT are separated by ≥3 cm and none >7 cm in greatest dimension. • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • Life expectancy of ≥12 weeks. • Adequate liver and kidney function. • Adequate blood cell count. • Female subjects must either be of non-reproductive potential or must have a negative serum pregnancy test upon study entry. • See Section 4.1 for durvalumab-specific requirements.
Exclusion Criteria: • Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). • Previous enrollment in the present study. • Any previous treatment with a PD-1 or PD-L1 inhibitor including durvalumab.

- Prior RT to any lesion that would receive RT on this protocol.
- Prior RT that could lead to an unacceptably high risk of clinically significant normal tissue injury due to high cumulative normal tissue dose as determined by the investigator.
- Subjects who have received more than 1 line of chemotherapy in the metastatic setting.
- History of another primary malignancy except for: 1) malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of study drug and of low potential risk for recurrence; 2) adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; 3) adequately treated carcinoma in situ without evidence of disease (e.g., cervical cancer in situ).
- Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤14 days prior to the first dose of study drug.
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
- Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
- Any unresolved toxicity (>grade 2, CTCAE version 4.03) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).
- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Graves' disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency.
- History of allogeneic organ transplant.
- History of liver cirrhosis and Child-Pugh class B or C.
- History of hypersensitivity to durvalumab or any excipient.

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
- Known history of previous clinical diagnosis of tuberculosis.
- History of leptomeningeal carcinomatosis.
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.
- Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
- Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
- Subjects with uncontrolled seizures.
- Subjects with known radiation hypersensitivity syndromes such as Ataxia-Telangiectasia or Nijmegen Breakage Syndrome
- See Section 4.2 for durvalumab-specific requirements

Investigational Product(s), Dose and Mode of Administration:

Durvalumab 1500 mg Q4W (equivalent to 20 mg/kg Q4W) IV infusion if ≥30 kg.
If patient is <30 kg, weight-based dosing should be used (see Appendix A).

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Grade 3-5 (G3-5) acute non-hematologic toxicity

Efficacy Assessments:

Progression-free survival (PFS)

Statistical Methods and Data Analysis:

This study will test the early toxicity and efficacy of durvalumab and RT in metastatic pancreas cancer patients who have progressed through first-line chemotherapy. This is a single-arm phase II trial with continuous monitoring of acute non-hematologic toxicity with the primary endpoint of progression free survival. Efficacy will be evaluated by time to progression or death, whichever comes first, and compared to historical control of chemotherapy alone as reported in the literature.

While the safety profile of durvalumab as a single agent has been established, the safety profile of durvalumab and RT is unknown. In case the defined boundary for the incidence of severe acute non-hematologic toxicity is crossed, the trial will be stopped, and the available data at that point will be carefully reviewed in order to suggest potential modification of the drug-radiation combination that may warrant testing in a future, independent trial.

Continuous toxicity monitoring in the first 20 patients enrolled (stopping rule)

The endpoint is severe (G3-5) acute non-hematologic toxicity. G3-5 non-hematologic occurs in <10% of patients treated with the anti-PD-1/PD-L1 mAb alone(Robert, Ribas et al. 2014). Early stopping for unexpected, severe early toxicity is based on continuous monitoring of G3-5 toxicity with the aim of keeping the probability of early stopping at around 5% if the true underlying rate of this toxicity is 10%. Following Ivanova et al.(Ivanova, Qaqish et al. 2005), we use the boundary proposed by Pocock(Pocock 1977). Values of b_k for the current design are given in Table 1.

Table 1. Pocock boundary for early stopping due to grade 3+ toxicity with a probability of stopping of about $\phi = 0.05$ and assuming the true toxicity rate is $\theta_0 = 0.1$

k	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
$\mathbf{b_k}$	–	2	3	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6	6	6

It is important for the validity and practical implementation of this strategy that the sequence of patients entered into the study is strictly recorded and preserved. Ideally, the design assumes that the outcome, i.e. the incidence of G3+ toxicity among the first *i* patients is known when entering patient *i+1*. The accrual rate is expected to be around 1-2 patients per month and the time window for observing early toxicity in a patient is pragmatically defined as the time during and within 2 weeks after the completion of RT; therefore, insisting on complete observations before entering the next patient will slow down accrual considerably. Instead we will allow staggered entry of cases. For patient safety reasons, no more than 6 patients will be allowed to be on active treatment at any point during continuous toxicity monitoring of the first 20 enrolled patients.

If the boundary is crossed, the treatment with durvalumab and RT will be discontinued in all patients on treatment at that point in time.

If 20 patients are enrolled and have completed therapy without crossing the toxicity boundary, this component of the trial will be concluded and the outcome will be reported. Accrual will be continued with respect to the phase II efficacy question, although toxicity will still be recorded and reported for the whole phase II cohort.

The chosen design parameters for the continuous toxicity monitoring portion of the trial have been chosen to give a high probability of stopping the study in case of unexpectedly high risk of toxicity.

The probability of early stopping is 4.9% if the true incidence of G3+ toxicity is 10%; the probability of early stopping is >99% if the true incidence of G3+ toxicity is 50% or more.

Primary efficacy analysis

All patients entered are evaluable with respect to the efficacy endpoints. The primary endpoint is PFS. The benchmark median PFS for metastatic pancreatic adenocarcinoma who have progressed through first line chemotherapy is 3 months(Oettle, Riess et al. 2014).

Sample Size Determination:

The expected accrual rate is 18 patients per year and we add a 12-months maturation period after completing accrual. Patients enrolled during the continuous toxicity monitoring component of the trial will all be included in the efficacy analysis. We will use a 1-sided test with a 5% significance level (α) to test the uni-directional hypothesis that the median PFS is prolonged from 3 to 4.5 months by combining RT combined with durvalumab in metastatic pancreas cancer patients who have progressed through first-line chemotherapy. With a statistical power (1-β) of the study of 80%, we estimate an accrual time of 26 months for a total sample size of 39 patients. All patients will be analyzed according to a strict intention-to-treat principle. The efficacy result will be summarized as a median PFS with a 1-sided 95% confidence interval. No early stopping rule for futility is planned due to the relatively rapid enrollment of patient in relation to the expected median PFS.

SCHEDULE OF STUDY ASSESSMENTS

Schedule of study assessments: Screening and Treatment Period (12 months: maximum of 13 doses, last infusion week 49)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**PD-L1 status evaluation**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**				
			Baseline	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1**	**Day 1 of the week**			
Week	**-6 to -1**	**-4 to -1**	**0**	**2, 4, 6, 8, 10, 12, etc**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**
				(±3 days)		**(±7 days)**	
Written informed consent/assignment of subject identification number	X						
Preliminary eligibility fulfilment (investigator's opinion)	X						
Demography and history of tobacco and alcohol use		X					
Previous treatments for pancreatic cancer		X					
Obtain archived or fresh tumour biopsy for PD-L1 assay (Section 8.3.3 further detail)[n]	X						
Formal verification of eligibility criteria		X					
Medical and surgical history		X					

Schedule of study assessments: Screening and Treatment Period (12 months: maximum of 13 doses, last infusion week 49)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**PD-L1 status evaluation**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**				
			Baseline	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1**	**Day 1 of the week**			
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				(±3 days)		**(±7 days)**	
Hepatitis B and C; HIV		X					
Serum βhCG[b]		X	As clinically indicated				
Durvalumab administration			X		X		
Radiation therapy				Days 15-17 (Week 2) Days 29-31 (Week 4)			
Physical examination[c]		X	X		X		
Vital signs (pre- during and post-infusion vital signs assessments including O2 sat)[d]		X	X	X			
Height		X					
Weight		X	X		X		
Electrocardiogram[e]		X	X then as clinically indicated				
Adverse event/serious adverse event assessment	X[l]	X	X		X (starting week 8)		
Concomitant medications		X	X		X (starting week 8)		
ECOG performance status		X	X		X		

Schedule of study assessments: Screening and Treatment Period (12 months: maximum of 13 doses, last infusion week 49)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**PD-L1 status evaluation**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**				
			Baseline	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
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				(±3 days)		**(±7 days)**	
Liver enzyme panel[f]				X			
Serum Chemistry (complete clin chem. panel including Liver enzymes)[f]		X	X		X		
Thyroid function tests (TSH and fT3 and fT4)[g]			X		X		
Hematology[f]		X	X		X		
Urinalysis[h]		X			X		
Coagulation parameters[i]		X	As clinically indicted				
CA 19-9		X	X		X		
Blood collection for correlative studies[m]			X	Days 1 (same day as baseline), 15, 29, 52 (see also Appendices B and C for 30 day post last dose Durvalumab blood draw)			
Blood collection for Future Biomedical Research[m,n]			X	Days 1 (same day as baseline), 52 (see also Appendices B and C for 30 post last dose Durvalumab day blood draw)			

Schedule of study assessments: Screening and Treatment Period (12 months: maximum of 13 doses, last infusion week 49)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**PD-L1 status evaluation**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**				
			Baseline	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**-42 to -1**	**-28 to -1**	**1**	**Day 1 of the week**			
Week	**-6 to -1**	**-4 to -1**	**0**	**2, 4, 6, 8, 10, 12, etc**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**
				(±3 days)		**(±7 days)**	
EORTC QLQ-C30 and EORTC QLQ-PAN26			X	X	X (starting week 8 thru week 52)		
CT scan chest, abdomen, pelvis with IV and oral contrast[j]		X				X	

[a] footnote deleted in previous version

[b] Pre-menopausal female subjects of childbearing potential only

[c] Full physical examination at baseline; targeted physical examination at other time points

[d] Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

[e] ECG during screening and at Day1 –baseline. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate others single. 1 ECG is needed while on treatment, and as clinically indicated. ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.

[f] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

[g] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[h] Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

[i] Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

[j] CT scans preferably with IV contrast, are collected during screening (for baseline) and as close to and prior to initiation of study treatment. Timing of on-treatment (follow-up) CT scans is every 8 weeks (± 1 week) until PD or off-study. Response according to RECIST 1.1 criteria (CR, PR) requires a confirmatory scan preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of CR, PR, or SD. Confirmation of PD for patients who are deemed clinically stable by the Investigator should be acquired preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of PD.

l For AEs/SAEs reported during prescreening additional information such as medical history and concomitant medications may be needed.

m Blood (approximately 4 teaspoons =20mL) will be drawn for correlative studies. Tumor and additional blood (approximately 2 teaspoons = 10mL) for future biomedical research (FBR) is optional, but patient consent must be obtained be prior to sample collection. If a patient does not consent for FBR then only blood for correlative studies will be drawn.

n Tumor tissue for PD-L1 analysis from fresh biopsy or archival tissue sample must be obtained before treatment begins. Biopsy or archival tissue must be obtained by core needle or excisional biopsy. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CBCT	cone beam computed tomography
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	peak concentration
Cmax,ss	peak concentration at steady state
Cmin	trough concentration
Cmin,ss	trough concentration at steady state

Abbreviation or special term	Explanation
CNS	central nervous system
CR	complete response
CT	computed tomography
CTV	clinical target volume
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice

Abbreviation or special term	Explanation
GTV	gross target volume
Gy	Gray
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IGTV	internal gross target volume
IHC	immunohistochemistry
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
mAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OAR	organ at risk
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
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

Abbreviation or special term	Explanation
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PTV	planning target volume
PVC	polyvinyl chloride
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	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RT	radiation therapy
SAE	serious adverse event
SD	stable disease

Abbreviation or special term	Explanation
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
t½	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to peak concentration
Tmax,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
WFI	water for injection
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease Background

In 2015, an estimated 49,000 people will be diagnosed with pancreatic cancer in the United States, and about 41,000 are likely to die of this disease(Siegel, Miller et al. 2015). Not only is pancreatic cancer a very deadly disease, the incidence of new cases is increasing such that it is estimated to become the second leading cause of cancer-related death by 2020 in the United States(Rahib, Smith et al. 2014). Because the majority of pancreatic cancer patients are either diagnosed with distant metastasis at initial diagnosis or eventually develop distant metastases, chemotherapy is a mainstay of treatment and can provide significant clinical benefit(Conroy, Desseigne et al. 2011). The long-term prognosis for metastatic pancreatic cancer patients is abysmal with 5-year survival rates less than 3% despite receiving aggressive systemic therapy.

Single-agent gemcitabine became the standard of care for advanced pancreatic cancer after resulting in superior overall survival, progression free survival, and quality of life compared to single-agent 5-fluorouracil (5-FU) in a randomized trial(Burris, Moore et al. 1997). Many subsequent trials attempted to further improve on clinical outcomes of single-agent gemcitabine, but the improvements that were seen did not seem to justify the increased toxicity of multi-agent chemotherapy regimens(Louvet, Labianca et al. 2005, Herrmann, Bodoky et al. 2007, Moore, Goldstein et al. 2007, Cunningham, Chau et al. 2009, Poplin, Feng et al. 2009). The current standard of care for metastatic pancreatic cancer in the first-line setting includes FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin)(Conroy, Desseigne et al. 2011) or gemcitabine plus nab-paclitaxel(Von Hoff, Ervin et al. 2013).

Metastatic pancreas cancer patients almost inevitably progress through first-line chemotherapy and many will receive second-line chemotherapy despite a lack of high-level evidence showing clinical benefit. A recently published phase III trial randomized patients who progressed through first-line gemcitabine monotherapy to best supportive care +/- OFF (oxaliplatin, leucovorin, 5-FU) although this trial was closed after enrolling only 46 out of a planned 165 patients due to poor accrual(Pelzer, Schwaner et al. 2011). Second-line overall survival in this study was improved in the OFF arm (4.8 vs 2.3 mo, p=.008). Progression free survival (PFS) and overall response rate (ORR) were not reported. The same authors modified the trial protocol and randomized patients to OFF vs. FF(Oettle, Riess et al. 2014). Results from 160 patients included longer median OS in the OFF arm (5.9 vs. 3.3 months; p=.01). OFF was also associated with improved PFS (2.9 vs. 2 months; p=.019). While these data hint at a benefit of second-line chemotherapy, there is no widely accepted standard of care therapy after progression through first-line chemotherapy for metastatic pancreas cancer. Novel effective therapies are clearly required.

Immunotherapy for pancreas cancer has recently attracted interest. While pancreas tumors have traditionally been thought to be poorly immunogenic with low levels of tumor infiltration lymphocytes (TILs), it is possible to induce greater immunogenicity within pancreas tumors to allow for effective immune-directed therapies(Lutz, Wu et al. 2014, Scholch, Rauber et al. 2015). Immune checkpoint inhibition, for example using anti-PD-L1 and anti-PD-1 monoclonal antibodies (mAb), has shown promise in multiple solid tumor types including pancreas cancer(Nomi, Sho et al. 2007, Sandin, Eriksson et al. 2014). On the other hand, some results from using immune checkpoint inhibitors alone for pancreatic cancer patients have been disappointing(Royal, Levy et al. 2010, Brahmer, Tykodi et al. 2012).

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. Programmed cell death ligand 1 (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(Mu, Huang et al. 2011), renal(Thompson, Gillett et al. 2005, Thompson, Kuntz et al. 2006, Krambeck, Dong et al. 2007), pancreatic(Nomi, Sho et al. 2007, Loos, Giese et al. 2008, Wang, Ma et al. 2010), ovarian cancer(Hamanishi, Mandai et al. 2007), and hematologic malignancies(Andorsky, Yamada et al. 2011, Brusa, Serra et al. 2013) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 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(Keir, Butte et al. 2008, Park, Omiya et al. 2010). 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(Zou and Chen 2008).

Because some data suggest that immune checkpoint blockade alone may be insufficient to generate a robust anti-tumor immune response in pancreatic cancer patients, it is reasonable to combine immune checkpoint blockade with other therapies that have strong effects on the immune system. The published literature consistently shows that RT can initiate and promote both innate and adaptive immunity against tumors by mechanisms including: 1) enhanced expression of damage associated molecular patterns (DAMPs)

leading to stimulation of dendritic cells and subsequent increase in antigen presentation; 2) enhanced expression of MHC class I molecules, adhesion molecules and stress-induced ligands, and death receptors on tumor cells leading to increased recognition and killing by T cells; 3) induction of chemokines CXCL9, CXCL10 and CXCL16 promoting recruitment of effector CD8+ T cells; and 4) release of pro-inflammatory cytokines such as interleukin 1β, TNFα, IFNγ driving anti-tumor immunity(Formenti and Demaria 2009, Formenti and Demaria 2013, Deng, Liang et al. 2014).

In fact, RT in combination with anti-PD-L1 mAb has shown synergy, with increased anti-tumor effect when compared to anti-PD-L1 mAb or RT alone in glioblastoma, colon, and mammary cancer mouse models(Zeng, See et al. 2013, Deng, Liang et al. 2014). For example Deng et al. demonstrated that RT plus anti-PD-L1 mAb caused an increase in antigen-specific CD8 T cells and decrease in MDSCs, leading to significantly increased anti-tumor effect compared to RT alone or anti-PD-L1 mAb alone, in a mammary cancer mouse model. Importantly, RT led specifically to increased PD-L1 expression in tumor cells additionally enhancing the effect of anti-PD-L1 mAb(Deng, Liang et al. 2014). Zeng et al performed a similar experiment in a glioblastoma mouse model and found that the combination of anti-PD-L1 mAb plus RT led to significantly increased cytotoxic CD8 T cells and decreased Tregs in the brains of the mice as well as prolonged survival compared to mice receiving RT or anti-PD-L1 mAb alone(Zeng, See et al. 2013). Additionally, tumor cells were injected in mice that had complete resolution of tumor after combination therapy and at 60 days no tumor growth was observed, suggesting that effective immunologic memory had developed. Therefore, there is optimism that a combination of RT and immune checkpoint inhibition can improve disease control for metastatic pancreatic cancer patients since they have no highly effective therapy options, especially after progression through first-line chemotherapy.

1.2 Durvalumab Background

Investigators should be familiar with the current durvalumab Investigator Brochure (IB Version 8.0)

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.

1.2.1 Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (IB Version 8.0)

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 (t1/2) 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.

1.2.2 Summary of clinical experience

Clinical experience with durvalumab is fully described in the current version of the durvalumab Investigator's Brochure (Version 8.0).

As of the DCO dates (15Apr2015 to 12Jul2015, Durvalumab IB Version 8.0), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

Pharmacokinetics and Product Metabolism

Study CD-ON-durvalumab-1108: As of 09 Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 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 09 Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

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, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. 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.

Adverse Event Profile of Durvalumab Monotherapy

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07 May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in

≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Efficacy

Study CD-ON-durvalumab-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease (SD) in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-durvalumab-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

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(Ng, Lum et al. 2006, Wang, Ma et al. 2010, Zhang, Shi et al. 2012, Narwal, Roskos et al. 2013). 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(Wang, Kang et al. 2014). 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(Zhang, Shi et al. 2012).

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 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 (Appendix A).

1.3 Research hypothesis

The vast majority of preclinical and clinical studies of RT and immunotherapy have only used one course of RT, either single fraction or fractionated. While this strategy is promising, especially based on exciting preclinical results showing dramatic synergy compared to RT or immunotherapy alone, there is reason to believe that the delivery of multiple RT courses may have an even more potent anti-tumor effect. When considering that RT is considered as an in situ tumor vaccine, in large part because it exposes the immune system to tumor neo-antigens, the rationale to use multiple RT courses is extrapolated from the response of the immune system to prophylactic vaccination against infectious disease. In the setting of vaccinations against infection a single inoculation is typically followed by multiple repeated inoculations (or “booster shots”) separated over time. Furthermore, vaccines against pancreatic cancer are commonly given with multiple boosters over several weeks to months.(Lutz, Yeo et al. 2011)

It has been well described that the first exposure of a foreign antigen leads to an initial antigen-specific immune response; subsequent exposure to the same antigen causes a more rapid and robust antigen-specific immune response(Owen, Punt et al. 2013). Likewise, exposure to the same antigen a third or even fourth time increases the efficacy of immune cells against that specific antigen and

decreases the time required for peak response. Therefore, the rationale for utilizing two courses of RT (instead of one) is that the first RT course may "prime" the immune system so that the second course may generate a secondary memory immune response that is more effective than the first. Another potential benefit of multi-course RT is that different tumor neo-antigens may be released from each of the two treated lesions, also leading to a more effective immune response by further expanding T-cell repertoire diversity.

The use of multi-course RT and immunotherapy was previously reported(Golden, Chhabra et al. 2015). Patients with metastatic cancer received 35 Gy in 10 fractions to two separate metastatic lesions with concurrent granulocyte-macrophage colony-stimulating factor (GM-CSF). Serious toxicities were uncommon. Immunomonitoring was not performed so the immunologic effect of the second RT course was not able to be specifically evaluated. Still, abscopal responses were observed in approximately 25% of patients. Given the development of modern immunotherapies such as immune checkpoint inhibitors there is reason to believe that an even higher rate of response may be seen if using multi-course RT and durvalumab.

1.4 Rationale for conducting this study

While a robust interaction between RT and immune checkpoint inhibitors has been repeatedly demonstrated in preclinical studies and has been suggested in clinical reports, it remains unclear what the optimal delivery for RT is to promote an anti-tumor immune response. There is ongoing investigation to determine what the appropriate number of fractions and the dose per fraction should be; this likely varies between tumor types and is dependent on the specific immunotherapy being used in combination.

Another question is whether treating several lesions with RT can lead to a strong immune response compared to treating a single lesion with a single course of RT. While multi-course RT may effectively control tumors, there are concerns about the added toxicity of RT and immunotherapy. Both can lead to inflammation-related adverse effects including colitis, hepatitis, and pneumonitis. While it does not appear that combining one or multiple courses of RT with immunotherapy results in an unacceptably high incidence of significant toxicity, further evaluation is needed. Therefore, this study will first evaluate the safety of combining sequentially giving ionizing radiation to 2 lesions with concurrent durvalumab, and if it is well tolerated, will continue to evaluate treatment efficacy.

The radiation dose for the lesions is a dose that is commonly used in studies that combine radiation and immunotherapy. This dose has been shown to result in abscopal responses with immunotherapy.

1.5 Benefit/risk and ethical assessment

Patients with metastatic pancreatic cancer have an extremely poor prognosis, especially those who have progressed through first-line chemotherapy. These patients are clearly in need of novel therapies for disease control. The combination of RT and immunotherapy has the potential to provide significant benefit to these patients by at least prolonging the time to further disease progression, and also possibly causing significant tumor regression. While this is expected to be well tolerated, there is the potential for increased adverse effects over what has been observed using durvalumab monotherapy. RT may have similar adverse effects as durvalumab based on the region of the body receiving radiation dose. For instance, RT to a lung metastasis could lead to pneumonitis while RT To a liver metastasis could lead to hepatitis, both of which may also be seen with durvalumab.

2. STUDY OBJECTIVES

2.1 Primary objective

2.1.1 The primary objective will be to evaluate whether the combination of RT and durvalumab improves median PFS compared to historical control in metastatic pancreas cancer patients who have progressed through first-line chemotherapy. PFS is defined as the time from the date of durvalumab initiation to the date of pancreatic cancer progression or death, whichever occurs first. This is a clinically relevant and appropriate endpoint for a phase II trial and since there are no prior studies

using immune checkpoint blockade with concurrent RT for metastatic pancreatic cancer will allow for historical comparison to PFS using second-line chemotherapy.

2.2 Secondary objective(s)

2.2.1 To evaluate the toxicity profile of durvalumab and RT in metastatic pancreas cancer patients who have progressed through first-line chemotherapy and receive RT and durvalumab.

2.2.2 To evaluate OS in metastatic pancreas cancer patients who have progressed through first-line chemotherapy and receive RT and durvalumab.

2.2.3 To evaluate the best overall response rate (ORR) by RECIST 1.1 in metastatic pancreas cancer patients who have progressed through first-line chemotherapy and receive RT and durvalumab.

2.2.4 To evaluate the clinical benefit rate (CBR) by RECIST 1.1 in metastatic pancreas cancer patients who have progressed through first-line chemotherapy and receive RT and durvalumab.

2.2.5 To evaluate the time to in-field progression in metastatic pancreas cancer patients who have progressed through first-line chemotherapy and receive RT and durvalumab.

2.2.6 To evaluate the quality of life (QOL) as measured by questionnaires EORTC QLQ-C30 and EORTC QLQ-PAN26 in metastatic pancreas cancer patients who have progressed through first-line chemotherapy and receive RT and durvalumab.

2.3 Exploratory objectives

Hypothesis-generating post-hoc analysis will be carried out since our study will not be powered to formally test pre-defined subgroup analysis. The following will be explored:

2.3.1 Tumor PD-L1 expression

PD-L1 expression, using Ventana assay with SP263 antibody, will be evaluated on archival (less than 3 years old) or freshly biopsied pancreatic tumor obtained prior to study entry. Pancreatic biopsy can be of either the primary tumor or a metastatic tumor. PD-L1 expression is not required for study enrolment, but a correlation between greater treatment response to

immune checkpoint blockade and baseline PD-L1 expression has been reported in other cancer types including melanoma and non-small cell lung cancer. Whether this correlation exists for pancreatic cancer has not been well described so therefore we will retrospectively evaluate whether baseline PD-L1 expression correlates with efficacy endpoints.

2.3.2 Peripheral blood levels of CD8 T cells, regulatory T cells (Treg), and myeloid derived suppressor cells (MDSC)

CD8 T cells, Tregs, and MDSCs all play important roles in the mounted immune response against cancer. Cancer therapies like immunotherapy and RT are successful in large part because they cause an increase in cancer-specific CD8 T cell numbers while they decrease the activity and concentrations of Tregs and MDSCs. We will study whether the absolute levels and/or change in the levels of these cells in peripheral blood at various intervals before, during, and after treatment with durvalumab and RT are correlated with efficacy endpoints. Serum will be drawn for this analysis prior to starting durvalumab, after completion of RT to the first lesion, after completion of the RT to the second lesion, during week 8, and at the time the patient is taken off the study due to disease progression or unacceptable toxicity.

2.3.3 Future biomedical research

With patient consent, Miami Cancer Institute will conduct future biomedical research on blood and tumor tissue specimens collected during this clinical trial. This research may include but is not limited to genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

3. STUDY DESIGN

3.1 Overview of study design

This is a single-institution phase II trial of durvalumab combined with RT for metastatic pancreatic cancer patients who have progressed through first-line chemotherapy. Pancreatic cancer patients who have received second-line or greater chemotherapy in the metastatic setting are not eligible. Target accrual is 39 patients. Durvalumab 1500 mg (or 20 mg/m2 if <30 kg) IV Q4W will be

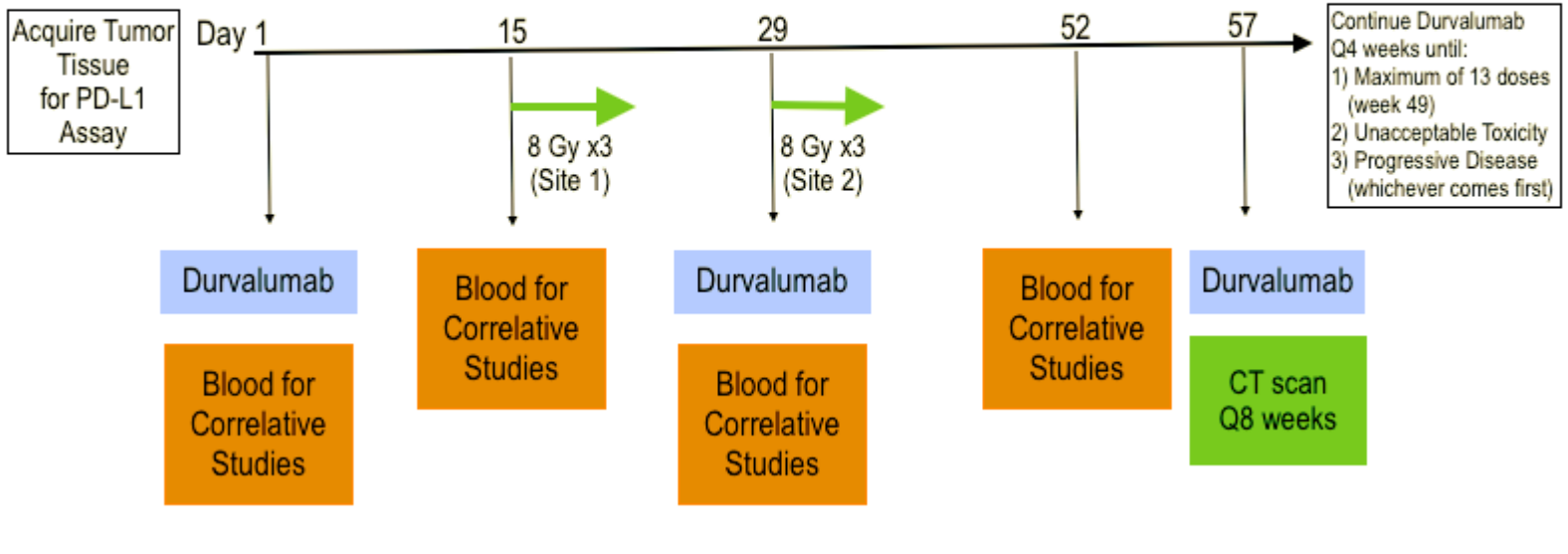
started and continued during RT and afterwards until the patient experiences either unacceptable toxicity or disease progression, whichever comes first. Patients must have at least two radiographically measurable pancreatic cancer lesions in different organs that have not previously received RT. Eligible lesions include either the primary pancreatic tumor in unresected patients or distant metastatic lesions. 8 Gy x 3 will be prescribed to one lesion during Week 3. 8 Gy x 3 will be prescribed to the second lesion during Week 5.

There will be continuous toxicity monitoring for the first 20 enrolled patients. If an excess of grade 3 or higher non-hematologic toxicities are seen in these initial patients, then the study will be closed early. Otherwise, accrual will be continued with respect to the phase II efficacy question, although toxicity will still be recorded and reported for the whole phase II cohort. The benchmark median PFS for metastatic pancreatic cancer patients receiving second-line chemotherapy is 3 months(Oettle, Riess et al. 2014). All patients will be analyzed according to a strict intention-to-treat principle. No early stopping rule for futility is planned due to the relatively rapid enrollment of patient in relation to the expected median PFS.

3.2 Study schema

Figure 1. Study flow chart

Schema


Acquire Tumor Tissue for PD-L1 Assay
Day 1
15
29
52
57
Continue Durvalumab Q4 weeks until:
1) Maximum of 13 doses (week 49)
2) Unacceptable Toxicity
3) Progressive Disease (whichever comes first)
8 Gy x3 (Site 1)
8 Gy x3 (Site 2)
Durvalumab
Blood for Correlative Studies
Durvalumab
Blood for Correlative Studies
Blood for Correlative Studies
Durvalumab
CT scan Q8 weeks
Blood for Correlative Studies

3.3 Study Oversight for Safety Evaluation

Early stopping for unexpected grade 3 or higher (G3+) acute toxicity is based on continuous monitoring of toxicity with the aim of keeping the probability of early stopping at around 5% if the true underlying rate of this toxicity is 10%. Following Ivanova et al.(Ivanova, Qaqish et al. 2005), we use the boundary proposed by Pocock(Pocock 1977). Values of b_k for the current design are given in Table 1.

Table 1. Pocock boundary for early stopping due to grade 3+ toxicity with a probability of stopping of about ϕ = 0.05 and assuming the true toxicity rate is $\theta_0 = 0.1$

k	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
b_k	–	2	3	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6	6	6

It is important for the validity and practical implementation of this strategy that the sequence of patients entered into the study is strictly recorded and preserved. Ideally, the design assumes that the outcome, i.e. the incidence of G3+ toxicity among the first *i* patients is known when entering patient *i+1*. Reduction of the dose of the study agent in an individual patient should only be performed if the patient develops G3+ toxicity. However, the accrual rate is expected to be around 1-2 patients per month and the time window for observing early toxicity in a patient is pragmatically defined as the time during and within two weeks after the completion of RT; therefore, insisting on complete observations before entering the next patient will slow down accrual considerably. Instead we will allow staggered entry of cases. For patient safety reasons, no more than 6 patients will be allowed to be on active treatment at any point during the continuous toxicity monitoring of the first 20 patients enrolled on the trial.

If the boundary is crossed, the treatment with durvalumab and RT will be discontinued in all patients on treatment at that point in time.

4. SUBJECT SELECTION

4.1 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations

2. Age ≥ 18 years at time of study entry.

3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

4. Life expectancy of ≥12 weeks as estimated by the investigator.

5. Biopsy-proven metastatic pancreatic adenocarcinoma with progression through standard first-line chemotherapy. Chemotherapy given as part of prior chemoradiation in the setting of non-metastatic pancreatic cancer does not count as a line of therapy.

6. At least 3 radiographically distinct pancreatic cancer lesions that are measurable by RECIST 1.1 criteria, including 2 that are (eligible) for RT

7. No lesion that would receive RT >7 cm in greatest dimension.

8. Subjects must consent to all study procedures described in the protocol including radiographic evaluation and repeated blood draws.

9. Adequate normal organ and marrow function as defined below:

   – Hemoglobin ≥ 9.0 g/dL

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
- Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
- Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) 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:

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

10. Female subjects must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1. Male or female patients of reproductive potential need to employ two highly effective and acceptable forms of contraception throughout their participation in the study and for 90 days after last dose of study drug.

11. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrolment in the present study

3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab

4. Prior RT to any lesion that would receive RT on this protocol.

5. Prior RT that could lead to an unacceptably high risk of clinically significant normal tissue injury due to high cumulative normal tissue dose as determined by the investigator.

6. Subjects who have received second-line or later chemotherapy for metastatic pancreatic cancer (prior chemotherapy received in the non-metastatic setting does not count).

7. History of another primary malignancy except for:

   - Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of study drug and of low potential risk for recurrence

   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

   - Adequately treated carcinoma in situ without evidence of disease e.g., cervical cancer in situ

8. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤14 days prior to the first dose of study drug.

9. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction

10. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid

11. Any unresolved toxicity (>grade 2, CTCAE version 4.03) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy.

12. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1

13. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

14. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)

15. History of primary immunodeficiency

16. History of allogeneic organ transplant

17. History of liver cirrhosis and Child-Pugh class B or C

18. History of hypersensitivity to durvalumab or any excipient

19. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses, any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent

20. Known history of previous clinical diagnosis of tuberculosis

21. History of leptomeningeal carcinomatosis

22. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab

23. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control

24. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

25. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.

26. Subjects with uncontrolled seizures.

27. Subjects with known radiation hypersensitivity syndromes such as Ataxia-Telangiectasia or Nijmegen Breakage Syndrome.

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of durvalumab

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
4. Pregnancy or intent to become pregnant
5. Any AE that meets criteria for discontinuation as defined in Section 6.6
6. Grade ≥ 3 infusion reaction
7. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
8. Initiation of alternative anticancer therapy including another investigational agent
9. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1 and Appendix B or C, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every month as an alternative.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

4.4 Replacement of subjects

Any subject that discontinues participation in this trial for any reason other than unacceptable toxicity or progressive disease before the initial efficacy evaluation (CT scan 2 months after initiation of durvalumab) may be replaced. These cases will be recorded and accounted for in the report of the trial.

5. INVESTIGATIONAL PRODUCTS

5.1 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.

5.1.1 Formulation/packaging/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.

5.1.2 Durvalumab Doses and treatment regimens

Durvalumab will be given intravenously at a dose of 1500mg (or 20mg/kg if the patient weighs <30 kg) IV Q4W for all patients. Durvalumab commences on Day 1 following confirmation of eligibility into the study and may be given for a maximum duration of treatment of 12 months (maximum of 13 doses, last infusion on week 48). Study treatment should be discontinued prior to 12 months if there is confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

Subjects who have a dose interruption due to toxicity at any point may resume treatment and complete the 12-month treatment period.

5.1.3 Study drug preparation

For patients weighing ≥ 30 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W), should be prepared. For subjects <30 kg body weight, dose is determined using body mass, calculating the stock volume of durvalumab to achieve the accurate dose according to Appendix A.

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 1500 mg 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 (i.e., 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.

For patients <30 kg, calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose according to Appendix A.

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.

Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined above, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

5.1.4 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 1 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.

5.1.5 Accountability and dispensation

Drug accountability records must be maintained according to good clinical practices. It is the responsibility of the investigator to ensure that the investigational products are only dispensed to eligible study participants.

5.1.6 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

5.2 Radiation Therapy

The primary intent of RT in this study is to augment a pancreatic cancer-specific immune response when given with durvalumab. While RT is commonly used to treat symptomatic focal lesions in metastatic cancer patients, the presence of symptomatic lesions is not a requirement for RT in this study.

The 2 lesions that will receive RT will be identified prior to starting study therapy. Appropriate subjects will have at least 2 pancreatic cancer lesions that meet all of the following criteria:

1) are measurable by RECIST 1.1,

2) are separated by at least 3 cm,

3) are each <7 cm in greatest dimension,

4) have not previously received RT,

5) are located in different organs (liver metastases are the only exception provided there are no other eligible lesions in other organs).

. If multiple lesions are present that meet these criteria, it is preferred that RT be given to lesions in different organs and if possible to the largest 2 lesions unless the investigator feels that treating other lesions would be of greater clinical significance such as for palliation of symptoms (provided they meet the criteria listed above).

5.2.1 Dose fractionation

The dose to both irradiated lesions will be 24 Gy delivered in 3 daily consecutive fractions of 8 Gy each prescribed to the isodose line covering 95% of the PTV. The rationale for this dose fractionation is because lower doses may not be as effective as stimulating an immune response, and higher doses would increase the risk of normal tissue toxicity (especially that of the liver and bowel) since the majority of patients are expected to receive RT to the abdomen on this study given the high incidence of liver metastasis from pancreatic cancer. Furthermore, published preclinical and clinical studies have demonstrated efficacy of this dose fractionation regimen with immunotherapy.(Dewan, Galloway et al. 2009, Golden, Demaria et al. 2013)

5.2.2 Technical Factors

Only photon therapy is permitted and energies ≥6MV are required. Cobalt-60, electron, and charged particle therapies are not permitted. Treatment for each lesion should begin on a Monday and finish on a Wednesday when possible. RT is scheduled to be delivered daily on Days 15-17 and Days 29-31.

Because multiple lesions will sequentially receive RT, multiple isocenters should be used with each centered on a separate lesion.

Composite plans should be generated to account for normal tissue dose from each lesion that is treated. Dose summation from multiple treatment sites should be determined on a single CT scan that encompasses the relevant anatomic region. A planning CT dataset that includes all targets and relevant critical structures in the imaging study should be obtained when possible. When this is not possible due to the size of the imaging study, CT datasets should be divided into two parts and treatment fields should be adjusted

so that dose spillage from the treatment of targets in one dataset to the next is minimal such that the dose contributions do not require summation.

5.2.3 Localization, Simulation, and Immobilization

Immobilization

Patients should be positioned in stable position that would facilitate daily setup reproducibility. It is anticipated that most patients will be immobilized in the supine position although the prone position may be considered to displace the small bowel away from the target. Patient immobilization should be established so that the gross tumor volume (GTV) does not extent outside of the planning treatment volume (PTV). Positioning patients on flat couches and relying solely on image-guidance for reproducible set-up is strongly discouraged.

Simulation

All patients will have CT-based treatment planning in a custom-made immobilization device prior to radiation therapy. CT simulation will be done once for both lesions that will receive RT. CT simulation should be performed ~1 week prior to initiation of the first course of RT. The CT simulation scan should be obtained with uniform slice thickness of ≤3 mm and should include the targeted lesions in addition to any relevant organs at risk (OARs), defined below. Both lesions that will receive RT and relevant OARs must be included in the simulation scan; treatment planning for both will be done using the same scan prior to starting RT. A second CT simulation scan will not be done specifically for the second course of RT. While it is ideal to treat both lesions in the same treatment position, if both lesions are not in the same region it is acceptable to use different treatment positions for each lesion if this would decrease OAR dose and/or improve daily treatment setup reproducibility. Thus, more treatment positions can be used at the discretion of the treating radiation oncologist, but every effort should be made to obtain composite dose distribution.

IV contrast must be used for CT simulation prior to treatment of an intact primary tumor in the pancreas and liver metastases, but may be used at the discretion of the treating physician for metastases involving other sites. For example, IV contrast may be omitted for treatment of a peripheral lung metastasis. IV contrast from the planning dataset is recommended to be converted to water equivalent density for planning. Oral contrast may be used at the discretion of the treating physician.

Respiratory Motion Assessment and Management

4D CT scan, implanted fiducial marker, and/or fluoroscopy should be used at the time of simulation for any targeted lesion that will move as a result of respiration. Motion management techniques including abdominal compression, active breathing control, end expiratory gating, or fiducial marker tracking should be strongly considered for any lesion with cranial-caudal motion of >10 mm. Fiducial markers are not required but should especially be considered for assessing motion of liver metastases and are recommended to be implanted 1-4 days prior to CT simulation by either CT or endoscopic guidance. Ideally at least 3 fiducial markers should be implanted in normal tissue within 1 cm of the periphery of the target lesion and each separated by at least 1-2 cm in different planes.

Daily Image Guidance

Daily imaging is needed to use a limited margin for setup uncertainty. This limited margin is necessary to reduce the volume of tissue receiving radiation, which could be detrimental to immune cells being recruited to the tumor. Image guidance will also be used for daily treatment setup accuracy. Prior to delivery of each fraction, daily kilovoltage (kV) imaging followed by cone-beam CT (CBCT) will be done. If fiducial markers are present, alignment should be to the fiducial markers. If fiducial markers are not present, then alignment should be to soft tissue within the treatment field.

5.2.4 Target Volumes and Treatment Planning

Target Volumes

The gross target volume (GTV) is defined as disease visible on CT scan. Because no additional margin will be used to encompass microscopic disease, a CTV will be not used. For targets that move with respiration, an IGTV should be created. This may be done using either the expiratory/inspiratory phase scans or from reconstructed maximum intensity projection (MIP) scans. A 3-5 mm uniform expansion from the GTV/IGTV will be used to create the PTV.

Treatment Planning

The use of stereotactic body radiation therapy (SBRT) is encouraged to meet normal tissue dose constraints for most targeted lesions. However, if it is possible to meet normal tissue dose constraints AND in the opinion of the treating radiation oncologist it is safe to use 3D conformal radiation therapy (3DCRT) instead of SBRT, then 3DCRT may be used to treat one or both targeted lesions.

When using an SBRT technique:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically 7-13 static radiation beams are used.
- A minimum field dimension of 3 cm should be observed when treating small lesions.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span at least 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e. no additional "margin" for dose buildup at the edges of the blocks of MLC jaws beyond the PTV). The only exception will be when observing the minimal field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% of the PTV will generally be 80-90% but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is generally equal to the prescription dose divided by the prescription isodose line (i.e., 24 Gy/0.6 = 40 Gy when 24 Gy is prescribed to the 60% isodose line).
- Doses higher than the prescription isodose (hot spots) should be manipulated to occur within the target.
- **Normalization:** The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV. While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.
- **Prescription Isodose Surface Coverage**: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be ≥ 60% and ≤90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan.
- **Target Dose Heterogeneity**: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR. Any dose >105% of the prescription dose should be located within the PTV and not within OARs.
- **Critical Organ Doses**: Respect all critical organ dose-volume limits listed below
- **High-Dose Spillage:**

  a. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV. See Figure 6-3

  b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.

i. The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio.
ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in the table below. Because it may become more difficult to restrict the 50% isodose volume when dose is summed from treatment of multiple metastases, this ratio should be evaluated for dose calculated for a single metastasis (i.e., not for composite dose). Additionally, the 50% isodose volume may be elongated deliberately in order to avoid OAR thereby making it difficult to meet the guidelines in the table below. This is acceptable as long as normal tissue constraints are met.

PTV volume (cc)_	Ratio of 50% Prescription Isodose volume to PTV volume, R50%	Maximum Dose at 2 cm (D2cm) from PTV in any direction as % of Prescribed Dose
1.8	< 7.5	<57.0
3.8	< 6.5	<57.0
7.4	< 6.0	<58.0
13.2	< 5.8	<58.0
22.0	< 5.5	<63.0
34.0	< 5.3	<68.0
50.0	< 5.0	<77.0
70.0	< 4.8	<86.0
95.0	< 4.4	<89.0
126.0	< 4.0	<91.0
163.0	< 3.7	<94.0

- Given that conformal tumor coverage is often more difficult to achieve in lung than in more homogeneous organs, these ratios should serve as a guide for liver, abdominal-pelvic, mediastinal/cervical metastases as well.
- iv. Elliptically shaped metastases as well as extremity metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected.

- v. These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm results in the inability to meet a conformity ratio of 1.5. Treatment planning should include tissue heterogeneity corrections.

Organs at Risk

OARs must be contoured and the specific OAR will depend on the location of the lesion that is treated with radiation therapy. Generally, any OAR within 3 cm of the PTV should be contoured.

OAR contours should be generated as follows:

- Spinal cord: The spinal cord will be contoured starting at least 10 cm above the superior extent of the PTV and then on all slices to at least 10 cm below the inferior extent of the PTV.

- Cauda equina: The cauda equina starts at the inferior extent of the spinal cord (~L1/L2) and includes the spinal canal into the sacrum to the filum terminale.

- Sacral plexus: Includes the nerve roots from L5 to S3 on each side from the neuroforamina to the coalescing of the nerves at the obturator internus muscle.

- Esophagus: The esophagus will be contoured using mediastinal windows starting at least 10 cm above the superior extent of the PTV and then on all slices to at least 10 cm below the inferior extent of the PTV. All layers from the mucosa to the adventitia should be included.

- Trachea and ipsilateral bronchus: contouring of the trachea should begin at least 10 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the main bronchi. The ipsilateral main bronchus should be contoured until the first branches.

- Heart/pericardium: The heart will be contoured along with the pericardial sac starting superiorly at the level of the inferior aspect of the aortic arch and inferiorly to the apex of the heart.

- Ipsilateral brachial plexus: The ipsilateral brachial plexus includes the spinal nerves exiting the neuroforaminae on the involved side from around C5-T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If the PTVs of all irradiated lesions are >5 cm away from the brachial plexus, this structure does not need to be contoured.

- Total lung: The right and left lungs will be contoured as one structure. Contouring should be done using lung windows. The GTV should be excluded from this contour.

- Stomach: The entire stomach and its contents should be contoured as a continuation of the esophagus and terminating at the first part of the duodenum.

- Duodenum: The duodenum should be contoured as a continuation of the stomach and will end where the superior mesenteric artery crosses over the 3rd part of the duodenum.

- Small bowel: The small bowel will be contoured as identified by oral contrast, if present. The duodenum will be excluded. The small bowel contour should extent 2 cm cranial and caudal to the PTV.

- Large bowel: The large bowel contour should extend 2 cm cranial and caudal to the PTV.

- Rectum: The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus should be contoured.

- Bladder: This organ will be contoured as bladder wall exclusive of urinary contents.

- Ribs: Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

- Femoral heads: The ball of the head and socket joint should be contoured.
- Liver: The entire liver should be contoured.
- Kidney: Both right and left kidneys excluding the renal pelvis/collecting system will be contoured in their entirety.

OAR Constraints*

OAR	Volume	Dose (Gy)
Spinal cord	<0.03 cc <1.2 cc	22.5 13
Ipsilateral brachial plexus	<0.03 cc <3 cc	26 22
Cauda equina	<0.03 cc <5 cc	25.5 21.9
Sacral Plexus	<0.03 cc <5 cc	24 22.5
Trachea and Ispilateral Bronchus^	<0.03 cc	30

	<5 cc	25.8
Esophagus^	<0.03 cc	27
	<5 cc	17.7
Heart/Pericardium	<0.03 cc	30
	<15 cc	24
Skin	<0.03 cc <10 cc	33 31
Stomach	<0.03 cc	30
	<10 cc	22.5
Duodenum^	<0.03 cc	24
	<3 cc	20
	<10 cc	15
Small/large bowel^	<0.03 cc	34.5

	<20 cc	24
Rectum^	<0.03 cc <3.5 cc <20 cc	49.5 45 27.5
Bladder	0.03 cc	33
	<15 cc	16.8
Ureter	<0.03 cc	40
Penile Bulb	< 3 cc	25
Femoral Heads	<10 cc	24
Renal Hilum/ Vascular Trunk	<15 cc	19.5
Rib	<0.03 cc <5 cc	50 40
Total lung	<37% lung volume	11
	<15% lung volume	20

	<1500 cc	10.5
	<1000 cc	11.4
Ipsilateral kidney	<130 cc	12.3
Total kidney	<200 cc	15
Liver (minus GTV or IGTV)	<700 cc	17.1

*Derived from [54]

^Avoid circumferential radiation

5.2.5 Missed treatments

Missed treatments and treatment breaks should be entered into the treatment record. Any missed treatments should be made up so that the total prescribed radiation dose is delivered. This should be done as expeditiously as possible and must respect time needed off treatment for any patients who experience significant toxicity. Management of acute treatment-related toxicity is described in Table 1. More than one fraction should not be delivered per day to make up treatments although treatment on Saturday/Sunday is permitted.

6. TREATMENT PLAN

6.1 Subject enrollment

6.1.1 Subject enrollment

This is a single-arm open label trial. The investigator and subjects will know the study treatment. Subjects are not randomized. Subjects who discontinue from the study prior to the first scan for treatment efficacy assessment 8 weeks after start of durvalumab may be replaced.

6.1.2 Procedures for handling subjects incorrectly enrolled

Subjects who are incorrectly enrolled but have not initiated treatment should be withdrawn from the study. Subjects who are incorrectly enrolled and have initiated treatment may continue treatment at the discretion of the investigator.

6.2 Retreatment with durvalumab

Some patients who discontinue durvalumab may be eligible for retreatment with durvalumab up to 1 year according to the table below if the study remains open and the following criteria are met:

- Discontinued durvalumab after achieving a CR anytime during the study or achieving a CR, PR, or SD upon completing all 12 months of study treatment.
- Has clinical evidence of pancreatic cancer progression or recurrence as confirmed by the investigator.
- Has not received any other cancer treatment for pancreatic cancer progression/recurrence.
- Still meets inclusion and exclusion criteria for this study.

Patients who meet the above criteria will undergo trial screening as per Section 8.1.1 with the following exceptions:

- Another informed consent will not have to be signed.

- Repeat biopsy for evaluation of PD-L1 expression is not required.

Study discontinuation will be as described in Section 4.3.

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**All assessments to be performed pre-infusion unless stated otherwise**				
	Baseline	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**1**	**Day 1 of the week**			
Week	**0**	**2, 4, 6, 8, 10, 12, etc**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**
		(±3 days)		**(±7 days)**	
Durvalumab	X		X		
Physical examination	X		X		
Vital signs including O2 sat. (pre- during and post-infusion vital signs assessments)[d]	X	X			
Weight	X		X		
Adverse event/serious adverse event assessment	X	X	X (starting week 8)		
Concomitant medications	X	X	X (starting week 8)		
ECOG performance status	X		X		
Liver enzyme panel		X			

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**All assessments to be performed pre-infusion unless stated otherwise**				
	Baseline	**Every 2 weeks**	**Every 4 weeks**	**Every 8 Weeks**	**Every 12 weeks**
Day	**1**	**Day 1 of the week**			
Week	**0**	**2, 4, 6, 8, 10, 12, etc**	**4, 8, 12, 16, 20, etc**	**8, 16, 24, 32, 40 and 48**	**12, 24, 36, 48**
		(±3 days)		**(±7 days)**	
Serum Chemistry (complete clin chem. panel including Liver enzymes)[f]	X		X		
Thyroid function tests (TSH and fT3 and fT4)[g]	X		X		
Hematology	X		X		
Urinalysis			X		
Coagulation parameters	As clinically indicted				
CA 19-9	X		X		
EORTC QLQ-C30 and EORTC QLQ-PAN26	X		X (starting week 8 thru week 52)		
CT scan chest, abdomen, pelvis with IV and oral contrast				X	

6.3 Dosage and Administration

All subjects will receive durvalumab 1500 mg IV (or 20mg/kg IV if <30 kg) Q4W starting on Day 1. This will continue until a maximum of 13 administrations (48 weeks) of durvalumab is given, progressive disease, or unacceptable toxicity, whichever occurs first. The dose of durvalumab will not change during this study. Refer to Section 5.1.4 and 5.1.5 for details regarding administration and monitoring of administration of durvalumab. If the scheduled day of durvalumab administration is missed (e.g. patient illness, holiday, etc) then durvalumab administration should be given the next day possible, or at least within 3 days, and any delays in durvalumab administration should be as limited as possible.

6.4 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the continuous toxicity monitoring component of the trial. The period for evaluating DLTs will be from the time of first administration of durvalumab until completion of the continuous toxicity monitoring of the first 20 enrolled subjects who have been followed for four weeks after the last dose of radiation. Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period which is from the time of first administration of durvalumab until four weeks after the last dose of radiation. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN

- Any ≥Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc). These inflammatory reactions must be specific to a tumor-bearing organ and must respond to steroids.
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

6.5 Dose Modification and Toxicity Management

6.5.1 Durvalumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (see below).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (see Table 1, 2, and 3 below). Dose reductions are not permitted.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Tables 1, 2, and 3, , respectively.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.1.3. All toxicities will be graded according to NCI CTCAE v4.03.

Table 1. Immune Mediated Reactions Associated with Durvalumab (19Aug2016)

Dose Modifications	Toxicity Management
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/study 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/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **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 regimen 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. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	It is recommended that management of irAEs follows the guidelines presented in this table: – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). – 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 (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO 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 (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Table 1. Immune Mediated Reactions Associated with Durvalumab (19Aug2016)

Dose Modifications	Toxicity Management
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. 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	

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE Immune-related adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	**Any Grade**	General Guidance	**For Any Grade:** – 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 modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 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, then the decision to reinitiate study drug/study regimen 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 (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			(eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a] − 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 [eg, 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 (eg, oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:** – 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 (eg, disease progression, other medications, or 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 (stool frequency of <4 over baseline per day)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (stool frequency of 4 to 6 over baseline per day)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		be resumed after completion of steroid taper.	− If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 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 to 4 mg/kg/day started. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. **Caution:** it is 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 to 4 days. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − 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 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × 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:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** 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 if elevations downgrade to 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 ×	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 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.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – 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.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– 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 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – 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 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – 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 modifications.	**For Grade 1:**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 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 (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 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 such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For 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	**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 the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals,

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – 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 (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and 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. 3. Doses of prednisone are ≤10 mg/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 (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 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 IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1:** – 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 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Discuss with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For 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.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		For Grade 4: Permanently discontinue study drug/study regimen.	– If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that 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 (eg, disease progression, infections, metabolic syndromes or medications). 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 (eg, 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. – It is 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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – 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.	**For 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 (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is 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 consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			○ If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is 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 IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For 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 Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** − Discuss with study physician. − Recommend hospitalization. − Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			GUILLAIN-BARRE: o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

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

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; irAE Immune-related adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PCP ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Table 2. Infusion-related Reactions Associated with Durvalumab

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For 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 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.	**For Grade 1 or 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 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.

Table 3. Non-immune-mediated Reactions Associated with Durvalumab

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 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.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

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."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

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.

6.5.2 Radiation therapy toxicity evaluation and management

Acute radiation toxicities are those that occur within 90 days from therapy start and will be graded according CTCAE v4.03. Toxicities related to RT differ based on the location of the treated lesion(s) and are related to dose received by OARs near the targeted lesion. The majority of lesions that receive ER on this study are anticipated to be in the thorax and abdomen based on the patterns of spread of pancreatic cancer. The most common sites of distant metastases are the liver, abdominal peritoneum, and lungs. Accordingly, the most likely potential acute radiation adverse events include fatigue, dermatitis, pneumonitis, esophagitis, colitis, hepatitis, nausea, vomiting, anorexia, and diarrhea.

RT should be continued without interruption, if possible. Grade 3 or higher acute toxicity from RT is not expected and is not expected to lead to RT interruption. However, Grade 3 or higher acute toxicity may necessitate a treatment break. If a treatment delay for acute toxicity is required, the total radiation dose and dose per fraction will not be modified. Any missed radiation fractions should be made up as quickly as possible; if needing to give RT and durvalumab on the same day then the RT should be given first, if possible. It should be noted that any Grade 3-5 acute radiation toxicity counts toward the early stopping rule.

Patients will be evaluated by a radiation oncologist at least once weekly during RT (Weeks 2 and 4) for physical examination and toxicity evaluation. Patients will be seen at least every 4 weeks by a radiation oncologist or medical oncologist thereafter starting in Week 8.

Late toxicities are those that occur after 90 days of therapy start and will be graded according to CTCAE v4.03. Late toxicities, like acute toxicities, are related to dose received by OARs near the targeted lesion.

6.5.3 Toxicity management guidelines for combination treatment regimen

Acute toxicity attributable to RT and not durvalumab should be managed accordingly with optimal supportive care measures. If toxicity clearly related to RT and not durvalumab ≥Grade 3 is persistent, then a RT break is allowable until the toxicity decreased to <Grade 3. Durvalumab should be continued during the RT break provided that there are no documented toxicities from durvalumab that would necessitate holding durvalumab. If durvalumab is held due to toxicity attributed solely to the durvalumab, then the RT should also be held until durvalumab is resumed. Once durvalumab is resumed, RT should also be resumed.

In addition to the individual toxicity management guidelines for durvalumab and RT described above, Table 4 outlines what actions are recommended for the management of any potential overlapping toxicities that may occur following treatment with this combination (e.g., which agent should be modified first, etc.).

Table 1. Toxicity management for durvalumab and combination radiation therapy

Toxicity	Action durvalumab	Action radiation therapy
Pneumonitis	As per Table 1	Hold if durvalumab held and/or RT-related toxicity resolved to <Grade 3
Hepatitis	As per Table 1	Hold if durvalumab held and/or RT-related toxicity resolved to <Grade 3
Colitis	As per Table 1	Hold if durvalumab held and/or RT-related toxicity resolved to <Grade 3
Diarrhea	As per Table 1	Hold if durvalumab held and/or RT-related toxicity resolved to <Grade 3
Pancreatitis	As per Table 1	Hold if durvalumab held and/or RT-related toxicity resolved to <Grade 3

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

Contraception

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 investigational product, or for at least 90 days following the last infusion of Durvalumab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not 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 5.

- Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 5) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 2. Effective methods of contraception (two methods must be used)

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

[a] This is also considered a hormonal method.

Blood donation

Subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab.

Diet

Subjects should maintain their usual diet. No dietary modification is required with the exception of those required to manage an AE such as diarrhea.

7.2 Concomitant treatment(s)

7.2.1 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 7.2.2.

All concomitant medication will be recorded in the electronic study database including all prescription, over-the-counter, herbal supplement, and IV medications. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included in the electronic study database.

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

7.2.2 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. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Local surgical treatment of isolated lesions for palliative intent is acceptable. Palliative RT in addition to what is intended to be given on this study is strongly discouraged, especially prior to imaging assessment after 8 weeks of study therapy. The treating physician should determine whether additional RT is clinically indicated and whether other alternative management options are available. The treating physician should also assess whether additional RT would be well tolerated, taking into account prior radiation dose to OARs.

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 and intranasal 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 (i.e., 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.

Table 3. Prohibited and Rescue Medications	
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)	Should be used when necessary for all patients. Additional RT is strongly discouraged outside of the RT required on this study.

8. STUDY PROCEDURES

8.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Study Assessments during the screening and treatment period is provided following the Protocol Synopsis.

8.1.1 Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures

and imaging studies that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window. Pre-treatment tumor biopsy should be performed within the 28-day screening window. It is preferred that laboratory tests required for screening or entry be performed within 10 days prior to receiving the first dose of durvalumab.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Tumor biopsy (if archival tumor is not available)
- Review of prior/concomitant medications
- CT scan chest, abdomen, pelvis
- Clinical laboratory tests for:
    - Hematology (see Table 7)
    - Clinical chemistry (see Table 8)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies
    - Urinalysis (see Table 9)
    - CA 19-9

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Study Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

8.1.3 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for subjects who have completed durvalumab treatment and achieved disease control, or have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX B.

Assessments for subjects who have discontinued durvalumab treatment due to confirmed PD are presented in APPENDIX C.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, electrocardiogram, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Study Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

ECGs are required during screening, prior to starting study treatment on Cycle 1 Day 1, at 16 weeks or at least one time after starting study treatment, 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. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 8.1. 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. On Day 1 and Week 16, ECGs will be recorded within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. 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, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses (at dose levels of 10 mg/kg or less), the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

8.2.2 Clinical laboratory tests

Laboratory tests for screening or entry should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. If screening laboratory values are not acceptable for study enrollment per the inclusion/exclusion criteria, then subjects may not be enrolled; laboratory tests may be repeated and the subject may be enrolled if the values are acceptable per the study protocol. Otherwise subjects whose laboratory values are not deemed acceptable per the study protocol may seek off-protocol therapy. After study enrollment, the investigator should evaluate laboratory values that are outside of the reference range and a determination should be made whether this represents an AE.

The following clinical laboratory tests will be performed (see the Schedule of Study Assessments, Appendix B and Appendix C for the timepoints of each test):

- Coagulation parameters: Activated partial thromboplastin time and International normalised ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
    - Urine human chorionic gonadotropin
    - Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone
    - free T3 and free T4 only if TSH is abnormal
- Other laboratory tests
    - Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody
    - CA 19-9

Table 4. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Table 5. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
[b] At baseline and as clinically indicated

Table 6. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

8.2.3 Patient reported outcomes (PRO)

PROs will be measured by the EORTC QLQ-30 and EORTC QLQ-PAN26 questionnaires. Subjects will complete both questionnaires starting with the EORTC QLQ-30 questionnaire first. The questionnaires will be completed by all subjects prior to study therapy, every 2 weeks until Week 8, and then every 4 weeks thereafter. PRO questionnaires will be administered to the subject by a clinical research staff member who is knowledgeable about both questionnaires although the same research staff member is not required to be present each time. Both questionnaires will be administered on paper and this data will then be entered into the electronic study database by designated clinical research staff.

8.2.3.1 EORTC QLQ-C30

The EORTC QLQ-30 is a widely used cancer-specific health-related QOL assessment tool.(Quinten, Martinelli et al. 2014) It contains 30 items and measures 5 functional dimensions (physical, role, cognitive, social, emotional), 6 single items (appetite loss, constipation, dyspnea, financial impact, sleep disturbance, diarrhea), 3 symptom items (fatigue, pain, nausea/vomiting) and a global health and QOL scale.

8.2.3.2 EORTC QLQ-PAN26

The EORTC QLQ-PAN26 is one of the most widely used tools for measuring QOL in pancreatic cancer patients.(Fitzsimmons, Johnson et al. 1999, Hurt, Mukherjee et al. 2015) It comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes).

8.3 Tissue/Blood Collection, and Storage Guidelines

8.3.1 Biomarker/Pharmacodynamic Tissue sampling and evaluation methods

PD-L1 Testing

PD-L1 testing will be performed by immunohistochemistry using assay developed by Ventana using SP263 antibody.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.
- The preferred sample for PD-L1 testing is less than or equal to 3 months old. In cases where a sample less than 3 months old was not available, patients will undergo a new biopsy if considered clinically appropriate by their treating physician.
- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.

- When obtaining fresh tumor tissue is not clinically appropriate, archival samples may be utilized that were obtained within the past 3 years. When archival samples are used to assess PD-L1 status, the age of the sample / date of collection should be captured.

- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing
The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier (e.g., Miami Cancer Institute)
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells

- Total percent positivity of PD-L1 in infiltrating immune cells

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 expression level. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.

- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.

- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended
- Below is the suggested routine overnight processing schedule:

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.
- Each sample should be reviewed for:
    - Adequate fixation
    - Good preservation of morphology
    - Presence of tumor tissue
    - Histopathology consistent with indication
    - Greater than 100 tumor cells are required to determine PD-L1 expression level – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

Sectioning instructions

- Unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:

- A minimum of 5-10 x 4 micron (μm) thick, unstained sections should be provided for PD-L1 testing
- A new disposable microtome blade must be used for each block to prevent contamination between Slides are stable under these conditions for 6 months.
- patient samples
- Apply one section per slide to positively-charged Superfrost glass slides
- The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 expression level.

Once prepared for shipping, specimens should be sent for centralized PD-L1 testing to:

Department of Pathology
Baptist Hospital of Miami
8900 North Kendall Drive, MCVI 5th Floor
Miami, FL 33176
E-mail: AlixV@baptisthealth.net

8.3.2 Blood samples for correlative studies

Blood for correlative studies should be drawn at the time points detailed in the Schedule of Study Assessments (Pre-Treatment on Day 1, and on Days 15, 29, and 52). These specimens should be transported to the Protocol Support Laboratory at Miami Cancer Institute (See section 8.3.4). A 4 teaspoon blood sample will be required to fill two 10mL Sodium Heparin tubes. Sodium heparin tubes for this study are available from the Protocol Support Laboratory. Blood sample tubes to be inverted several times immediately after the blood draw. The tubes may be transported to the Protocol Support Laboratory at ambient Temperature. It is preferable for the research blood to arrive to the Protocol Support Laboratory within 1-2 hours of the blood draw.

8.3.3 Future biomedical research

If a patient consents to the optional future biomedical research, then at Pre-treatment, and on Days 1 and 52 the blood draw will include an additional2 teaspoons of blood to fill one 10mL Sodium Heparin tube as the correlative study blood draw. This sample is sent to the Protocol Support Laboratory. See the Schedule of Study Assessments. Blood sample tube to be inverted several times immediately after the blood draw and the tube may be transported to the Protocol Support Laboratory at ambient Temperature.

8.3.4 Blood Sample Processing and Storage

Specimens should be transported to the following address:

Protocol Support Laboratory
Miami Cancer Institute
8900 N Kendall Dr, 4R410
Miami, FL 33176
Email: MCIPSandBRF@baptisthealth.net

Please contact the Protocol Support Laboratory; Eneida Plaza at MCIPSandBRF@baptisthealth.net or eneidap@baptisthealth.netat the time of courier transport.

Samples should be processed by the lab within 30 minutes of collection. Once in the lab, blood will be diluted 1:1 with phosphate buffered saline (PBS) and then layered onto an equal volume of Lymphocyte Separation Media. The blood will then be centrifuged at 1500g for 30 minutes (no break) at room temperature within one hour of collection. The plasma will be removed, aliquoted, and labeled with the study number (GCC 1598), subject's study number, "plasma", volume and date, and frozen at -80C. The cells or "buffy coat" will then be removed, and placed into a new 15 cc conical tube. Ten ml of ice cold PBS will be added to the cells in the tube and then the tube will be inverted 5 times and centrifuged at 350g for 10-15 min at 4C. The tube will be gently inverted to pour off supernatant—the pellet should not be disturbed. Once the tube is upright the pellet will be dislodged by gently tapping the tube. Ten ml of ice cold phosphate buffered saline (PBS) will be added. The tube will be inverted five times, a 100ul aliquot

removed for counting, then centrifuged one last time at 350g for 10-15 min at 4C. Cells will be counted by trypan blue exclusion. After centrifugation, supernatant will be aspirated and the cells will be re-suspended to yield cells at 10-20 million cells per ml in freezing media (95% FBS / 5%DMSO). The viably frozen cells will be labeled with the study ID (GCC1598), subject's study ID, site ID, date and number of cells. The cells should be placed in a Mr. Frosty, if possible, in a -80C freezer.

8.3.5 Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 7. Volume of Blood to Be Drawn From Each Subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	**Clinical chemistry**	10	18	180
	Hematology	10	18	180
Liver function tests		5	12	60
Coagulation parameters		5	1	5
Correlative studies (PBMCs, MDSCs)		20	5	100
Future Biomedical Research		10	3	30
Total for duration of study				555 mL = 112.6 teaspoons = 2.3 cups "about 2 cups"

8.3.6 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

9.1.1 Tumor Imaging

Initial tumor imaging should be performed within 28 days prior to the start of durvalumab and every 8 weeks thereafter, or sooner if clinically indicated. A CT scan with IV and oral contrast of the chest, abdomen, and pelvis is required for initial tumor imaging and for all subsequent imaging. MRI scans are not permitted on this study.

The investigator must review baseline images to confirm the subject has measurable disease per RECIST 1.1. Subsequent images must also be reviewed for determination of treatment response. Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from durvalumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix B).

9.1.2 Definitions for Disease Assessment

Measurable lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least 10 mm on CT scan.

Malignant lymph nodes: To be considered measurable, a lymph node must be at least 15 mm by CT scan.

Non-measurable lesions: All other lesions <10 mm on CT scan.

Target lesions: Target lesions should be identified and measured at baseline. Target lesions include measurable lesions up to a maximum of two lesions per organ and up to five lesions in total that are representative of all involved organs. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and are to undergo reproducible repeated measurements. If the largest lesion does not lend itself to reproducible measurement it should not be considered a target lesion and instead the next largest lesion that can be measured reproducibly should be selected. A sum of the longest diameters for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

9.1.3 Evaluation of Disease Response

Response assessment will be made using RECIST 1.1.

Definition of response in target lesions:

- **Complete Response (CR):** Disappearance of all target lesions
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions compared to baseline sum of target lesions, or any new lesions
- **Stable Disease (SD):** Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD

Response should be confirmed by repeat CT scan that may be performed at the next regularly scheduled scan and no earlier than 4 weeks after imaging showing a particular response (unless clinically indicated).
Definition of response in non-target lesions

- **Complete Response (CR):** Disappearance of all non-target lesions
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
- **Incomplete Response/Stable Disease (SD):** Persistence of one or more non-target lesions

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok, Hoos et al. 2009, Nishino, Giobbie-Hurder et al. 2013).

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the following will be included in disease response evaluation in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab would continue between the initial assessment of progression and confirmation for progression.

- In addition, subjects may continue to receive durvalumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from durvalumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix B).

9.1.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence.

Table 11. Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	PR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

10.1.1 Safety Parameters

10.1.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE 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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-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.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

10.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

Results in death

Is immediately life-threatening

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability or incapacity

Is a congenital abnormality or birth defect in offspring of the subject

Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above. Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

The relationship of durvalumab and/or RT with the occurrence of each SAE should be determined as follows:

- Unrelated: There is no evidence of any causal relationship.
- Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).

- Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition).

- Probably: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

This determination should be made using the investigator's clinical judgment and should be recorded in the electronic study database.

10.1.3 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.

AESIs for durvalumab 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. 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 aetiology. 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 Physician.

AESIs observed with durvalumab include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- 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)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

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

10.1.4 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs(Topalian, Hodi et al. 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Section Table 1.

10.1.5 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy(Brahmer, Tykodi et al. 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute

allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 6.6.1.

10.1.6 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies(Brahmer, Tykodi et al. 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Section 6.6.1.

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

10.1.7 Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Table 1.

10.1.8 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Table 1.

10.1.9 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Table 1.

10.1.10 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 1.

10.1.11 Nephritis

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. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 1.

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.

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild) An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc.).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

Because both checkpoint inhibitors and radiation therapy both may result in inflammation-related adverse effects (e.g. pneumonitis, hepatitis) it may not possible to definitively assess the relationship between all inflammation-related adverse effects and either durvalumab or RT. It should be noted that adverse effects of radiation therapy are localized to the anatomic region/organ that receives radiation dose and does not cause clinically apparent inflammatory adverse effects at distant locations. For example, pneumonitis may be caused by either durvalumab or RT to a lung metastasis; however pneumonitis would not be caused by pelvic RT since there would be no significant radiation lung dose.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded by the case report forms/worksheets 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 criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

AE (verbatim)

The date when the AE started and stopped
Changes in NCI CTCAE v4.03 grade and the maximum CTC grade attained
Whether the AE is serious or not
Investigator causality rating against durvalumab (yes or no) and/or RT (yes/no)
Action taken with regard to durvalumab/RT
Outcome

In addition, the following variables will be collected for SAEs as applicable:
Date AE met criteria for serious AE
Date Investigator became aware of serious AE
Reason why AE is serious
Date of hospitalization
Date of discharge
Probable cause of death
Date of death
Autopsy performed
Description of AE
Causality assessment in relation to Study procedure(s)
Causality assessment in relation to RT and/or durvalumab

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab).

During the course of the study all AEs 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 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 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.

10.3.1.1 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the electronic study database. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10.3.1.2 Post study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator will notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

10.3.2 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must inform the FDA, via a MedWatch 3500A form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch 3500A report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor 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 at the same time.

***** A ***cover page*** should accompany the **MedWatch 3500A** 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-15 11078)

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:***
AEMailboxClinicalTrialTCS@astrazeneca.com
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.3.3 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported as follows:

Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented <<as events for survival analysis>>, but will not be reported as an SAE.

10.3.4 Overdose

An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this 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 and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). 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 (see Section 10.1.2 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

10.3.5 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- 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.

10.3.6 Pregnancy

10.3.6.1 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.

10.3.6.2 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 monotherapy.

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.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Statistical analysis plan summary

This study will test the early toxicity and efficacy of durvalumab 1500 mg (or 20 mg/m2) IV Q4W and RT to 2 separate lesions in metastatic pancreas cancer patients who have progressed through first-line chemotherapy. Radiation will be given to the same total dose (24 Gy) over 3 fractions to each lesion. This is a single-arm phase II trial with continuous monitoring of acute non-hematologic toxicity with the primary endpoint of progression free survival. Efficacy will be evaluated by time to progression or death, whichever comes first, and compared to historical control of chemotherapy alone as reported in the literature.

While the safety profile of durvalumab has been established when giving the drug as a single agent, the safety of combined durvalumab with ionizing radiation needs to be established. In case the defined boundary for the incidence of severe acute non-hematologic toxicity is crossed, the trial will be stopped, and the available data at that point will be carefully reviewed in order to suggest potential modification of the drug-radiation combination that may warrant testing in a future independent trial.

11.2 Statistical analysis plan

11.2.1 Continuous toxicity monitoring in the first 20 patients enrolled (stopping rule)

Continuous toxicity monitoring will occur for the first 20 patients enrolled. The endpoint is severe (G3-5) acute non-hematologic toxicity. G3-5 non-hematologic occurs in <10% of patients treated with the anti-PD-1/PD-L1 mAb alone(Robert, Ribas et al. 2014). Early stopping for unexpected, severe early toxicity is based on continuous monitoring of G3-5 toxicity with the aim of keeping the probability of early stopping at around 5% if the true underlying rate of this toxicity is 10%. Following Ivanova et al.(Ivanova, Qaqish et al. 2005), we use the boundary proposed by Pocock(Pocock 1977). Values of b_k for the current design are given in Table 1.

Table 1. Pocock boundary for early stopping due to grade 3+ toxicity with a probability of stopping of about ϕ = 0.05 and assuming the true toxicity rate is $\theta_0 = 0.1$

k	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
b_k	–	2	3	3	3	3	4	4	4	4	4	4	5	5	5	5	5	6	6	6

It is important for the validity and practical implementation of this strategy that the sequence of patients entered into the study is strictly recorded and preserved. Ideally, the design assumes that the outcome, i.e. the incidence of G3+ toxicity among the first *i* patients is known when entering patient *i+1*. The accrual rate is expected to be around 1-2 patients per month and the time window for observing early toxicity in a patient is pragmatically defined as the time during and within two weeks after the completion of RT; therefore, insisting on complete observations before entering the next patient will slow down accrual considerably. Instead we will allow staggered entry of cases. For patient safety reasons, no more than 6 patients will be allowed to be on active treatment at any point during the continuous toxicity monitoring portion of the trial.

If the boundary is crossed, the treatment with durvalumab and RT will be discontinued in all patients on treatment at that point in time.

If 20 patients are enrolled and have completed therapy without crossing the toxicity boundary, the continuous toxicity monitoring component will be concluded and the outcome will be reported. Accrual will be continued with respect to the phase II efficacy question, although toxicity will still be recorded and reported for the whole phase II cohort.

The chosen design parameters for the continuous toxicity monitoring portion of the trial have been chosen to give a high probability of stopping the study in case of unexpectedly high risk of toxicity. The probability of early stopping is 4.9% if the true incidence of G3+ toxicity is 10%; the probability of early stopping is >99% if the true incidence of G3+ toxicity is 50% or more.

11.2.2 Primary Efficacy Analysis

All patients entered are evaluable with respect to the efficacy endpoints. The primary endpoint is PFS. The benchmark median PFS for metastatic pancreatic adenocarcinoma who have progressed through first line chemotherapy is 3 months(Oettle, Riess et al. 2014).

The expected accrual rate is 18 patients per year and we add a 12-months maturation period after completing accrual. Patients enrolled during the continuous toxicity monitoring portion of the trial will all be included in the phase II efficacy analysis. All patients will be analyzed according to a strict intention-to-treat principle.

11.3 Determination of Sample Size

The efficacy result will be summarized as a median PFS with a 1-sided 95% confidence interval. We will use a 1-sided test with a 5% significance level (α) to test the uni-directional hypothesis that the median PFS is prolonged from 3 to 4.5 months by combining RT combined with durvalumab in metastatic pancreas cancer patients who have progressed through first-line chemotherapy. With a statistical power (1-β) of the study of 80%, we estimate an accrual time of 26 months for a total sample size of 39 patients. No early stopping rule for futility is planned due to the relatively rapid enrolment of patient in relation to the expected median PFS. The method used for sample size estimation assumes exponential survival distributions according to Dixon and Simon (Dixon et al. 1988)

11.4 Efficacy Endpoints

Primary

Progression free survival (PFS)**:** Progression free survival is defined as the time from the initiation of durvalumab to the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. If a patient recurs and is eligible for retreatment, then only the time to the initial recurrence will be included in the evaluation of PFS. Patients who are alive with no evidence of disease at the time of last contact will be censored at that date.

Secondary
Overall Response Rate (ORR): The overall response rate is defined as the percentage of the patients who have a complete response (CR) or partial response (PR) as defined by RECIST 1.1. The patient's best overall response rate defined as the best response recorded from the start of the treatment until disease progression will be recorded.

Clinical Benefit Rate (CBR) – The clinical benefit rate is the percentage of patients that have achieved a complete response, partial response, or stable disease as defined by RECIST 1.1.

Time to in-field progression – The time to in-field progression is defined as the time from initiation of treatment to progression of disease within the radiation field.

Overall Survival – Overall survival is defined as the time from first treatment until death. Patients who are alive will be censored at the last date of patient contact.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

12.2 Ethics and regulatory review

Study procedures may begin once IRB approval is secured and other details (e.g. study supplies, clinical trial agreements) are in place.

12.3 Informed consent

All subjects must sign informed consent to participate in and register for this study. The written informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative.

All subjects will be informed about the following:

- Study aims
- Possible adverse effects
- Study procedures
- Confidentiality of patient data
- Medical records potentially being reviewed by authorized individuals other than the treating physician

It will be emphasized to each subject that participation is completely voluntary and that all subjects have the right to refuse participation at any time. Doing so will not affect the patient's subsequent care.

12.4 Changes to the protocol and informed consent form

The study protocol may undergo changes after the start of the study. Changes to the study protocol that are considered to significantly affect the potential benefits and/or risks for study subjects should be communicated to the subjects. However, all amendments to the protocol are not required to be communicated to study subjects unless they are of direct clinical significance.

12.5 Audits and inspections

Regulatory agencies may audit or inspect the participating study sites at any time. Such an audit/inspection may consist of interviews with the principal investigator and/or study staff, review of study practices and documentation, and review of facilities and source data verification to assess compliance. Authorized individuals should be granted direct access to any and all documentation pertaining to the clinical trial including hospital patient chats and investigator study files.

13. STUDY MANAGEMENT

13.1 Monitoring of the study

13.1.1 Source data

Data safety and verification monitoring will be conducted in accordance with Miami Cancer Institute standard operating procedures and Data and Safety Monitoring Plan (DSMP), the Code of Federal Regulations (CFR), and FDA and International Counsel on Harmonization (ICH) E6 Guidelines.

13.1.2 Data Safety and Monitoring Committee (DSMC)/Quality Assurance Committee (QAC)

The Miami Cancer Institute DSMC/QAC will provide trial oversight per its standard operating procedures and Data and Safety Monitoring Plan (DSMP).

13.1.3 FDA Amendment and Annual Reporting

The FDA Annual Report will be submitted to the Agency by the Coordinating Center preferably 60 days ahead of the date on the IND approval letter/email. The Coordinating Center will submit major amendments to the FDA, AstraZeneca prior to submission to Baptist Health South Florida Institutional Review Board (IRB) for review and approval followed by performance site distribution. Minor amendments, e.g., CICERO Modifications for staff update, CICERO application updates, etc., will be reported to the FDA at the time of the next major amendment or at the next FDA Annual Report (whichever comes first).

13.2 Study timetable and end of study

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for subjects who have completed durvalumab treatment and achieved disease control, or have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX B.

Assessments for subjects who have discontinued durvalumab treatment due to confirmed PD are presented in APPENDIX C.

14. DATA MANAGEMENT

Clinical data will be entered into an electronic study database by the designated performance site personnel. This database will be maintained on a secured server at Miami Cancer Institute. Information should be entered in a way that is 21CRF11.10 (electronic medical records) compliant. All study data will be collected by the research team at each and every study visit and recorded in the electronic study database. All source documents will be obtained and retained along with any study forms, and placed into the patient's research record.

14.1 Records retention

Essential documents should be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records may be maintained in secure offsite storage after completion of study follow-up and data analysis.

14.2 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 Identity of investigational product(s)

Table 82. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	1500 mg, solution, IV	MedImmune

16. LIST OF REFERENCES

Andorsky, D. J., et al. (2011). "Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells." Clin Cancer Res **17**(13): 4232-4244.

Brahmer, J. R., et al. (2012). "Safety and activity of anti-PD-L1 antibody in patients with advanced cancer." N Engl J Med **366**(26): 2455-2465.

BACKGROUND: Programmed death 1 (PD-1) protein, a T-cell coinhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host's immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models. METHODS: In this multicenter phase 1 trial, we administered intravenous anti-PD-L1 antibody (at escalating doses ranging from 0.3 to 10 mg per kilogram of body weight) to patients with selected advanced cancers. Anti-PD-L1 antibody was administered every 14 days in 6-week cycles for up to 16 cycles or until the patient had a complete response or confirmed disease progression. RESULTS: As of February 24, 2012, a total of 207 patients--75 with non-small-cell lung cancer, 55 with melanoma, 18 with colorectal cancer, 17 with renal-cell cancer, 17 with ovarian cancer, 14 with pancreatic cancer, 7 with gastric cancer, and 4 with breast cancer--had received anti-PD-L1 antibody. The median duration of therapy was 12 weeks (range, 2 to 111). Grade 3 or 4 toxic effects that investigators considered to be related to treatment occurred in 9% of patients. Among patients with a response that could be evaluated, an objective response (a complete or partial response) was observed in 9 of 52 patients with melanoma, 2 of 17 with renal-cell cancer, 5 of 49 with non-small-cell lung cancer, and 1 of 17 with ovarian cancer. Responses lasted for 1 year or more in 8 of 16 patients with at least 1 year of follow-up. CONCLUSIONS: Antibody-mediated blockade of PD-L1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non-small-cell lung cancer, melanoma, and renal-cell cancer. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT00729664.).

Brusa, D., et al. (2013). "The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia." Haematologica **98**(6): 953-963.

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Conroy, T., et al. (2011). "FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer." N Engl J Med **364**(19): 1817-1825.

Cunningham, D., et al. (2009). "Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer." J Clin Oncol **27**(33): 5513-5518.

Deng, L., et al. (2014). "Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice." J Clin Invest **124**(2): 687-695.

Dewan, M. Z., et al. (2009). "Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti–CTLA-4 antibody." Clinical Cancer Research **15**(17): 5379-5388.

Dixon, DO and Simon, R: Sample Size Considerations for Studies Comparing Survival Curves using Historical Controls. J Clin Epidemiol Vol 41. No 12, pp 1209-1213.

Fitzsimmons, D., et al. (1999). "Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life." Eur J Cancer **35**(6): 939-941.

Formenti, S. C. and S. Demaria (2009). "Systemic effects of local radiotherapy." Lancet Oncol **10**(7): 718-726.

Radiotherapy is generally used to treat a localised target that includes cancer. Increasingly, evidence indicates that radiotherapy recruits biological effectors outside the treatment field and has systemic effects. We discuss the implications of such effects and the role of the immune system in standard cytotoxic treatments. Because the effects of chemotherapy and radiotherapy are sensed by the immune system, their combination with immunotherapy presents a new therapeutic opportunity. Radiotherapy directly interferes with the primary tumour and possibly reverses some immunosuppressive barriers within the tumour microenvironment-ideally, recovering the role of the primary tumour as an immunogenic hub. Local radiation also triggers systemic effects that can be used in combination with immunotherapy to induce responses outside the radiation field.

Formenti, S. C. and S. Demaria (2013). "Combining radiotherapy and cancer immunotherapy: a paradigm shift." J Natl Cancer Inst **105**(4): 256-265.

Golden, E. B., et al. (2015). "Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial." Lancet Oncol **16**(7): 795-803.

Golden, E. B., et al. (2013). "An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer." Cancer Immunol Res **1**(6): 365-372.

A posteriori evidence suggests that radiotherapy to a targeted tumor can elicit an immune-mediated abscopal (ab-scopus, away from the target) effect in non-targeted tumors, when combined with an anti-cytotoxic T-lymphocyte antigen-4 monoclonal (CTLA-4) antibody. Concurrent radiotherapy and ipilimumab (a human monoclonal anti-CTLA-4 antibody) induced immune-mediated abscopal effects in poorly immunogenic pre-clinical tumor models and metastatic melanoma patients. However, no such reports exist for patients with metastatic lung adenocarcinoma. We report the first abscopal response in a treatment-refractory lung cancer patient treated with radiotherapy and ipilimumab. A post-treatment increase in tumor-infiltrating cytotoxic lymphocytes, tumor regression, and normalization of tumor markers was observed. One year after treatment with concurrent radiotherapy and ipilimumab the patient is without evidence of disease.

Hamanishi, J., et al. (2007). "Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer." Proc Natl Acad Sci U S A **104**(9): 3360-3365.

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Krambeck, A. E., et al. (2007). "Survivin and b7-h1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma." Clin Cancer Res **13**(6): 1749-1756.

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Lutz, E., et al. (2011). "A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma. A Phase II trial of safety, efficacy, and immune activation." Ann Surg **253**(2): 328-335.

Lutz, E. R., et al. (2014). "Immunotherapy Converts Nonimmunogenic Pancreatic Tumors into Immunogenic Foci of Immune Regulation." Cancer Immunol Res **2**(7): 616-631.

Moore, M. J., et al. (2007). "Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group." J Clin Oncol **25**(15): 1960-1966.

Mu, C. Y., et al. (2011). "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 **28**(3): 682-688.

Narwal, R., et al. (2013). "Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus." Clin Pharmacokinet **52**(11): 1017-1027.

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New, effective therapies are needed for pancreatic ductal adenocarcinoma. Ipilimumab can mediate an immunologic tumor regression in other histologies. This phase II trial evaluated the efficacy of Ipilimumab for advanced pancreatic cancer. Subjects were adults with locally advanced or metastatic pancreas adenocarcinoma with measurable disease, good performance status, and minimal comorbidities. Ipilimumab was administered intravenously (3.0 mg/kg every 3 wk; 4 doses/course) for a maximum of 2 courses. Response rate by response evaluation criteria in solid tumors criteria and toxicity were measured. Twenty-seven subjects were enrolled (metastatic disease: 20 and locally advanced: 7) with median age of 55 years (27 to 68 y) and good performance status (26 with Eastern Cooperative Oncology Group performance status =0 to 1). Three subjects experienced >/= grade 3 immune-mediated adverse events (colitis:1, encephalitis:1, hypohysitis:1). There were no responders by response evaluation criteria in solid tumors criteria but a subject experienced a delayed response after initial progressive disease. In this subject, new metastases after 2 doses of Ipilimumab established progressive disease. But continued administration of the agent per protocol resulted in significant delayed regression of the primary lesion and 20 hepatic metastases. This was reflected in tumor markers normalization, and clinically significant improvement of performance status. Single agent Ipilimumab at 3.0 mg/kg/dose is ineffective for the treatment of advanced pancreas cancer. However, a significant delayed response in one subject of this trial suggests that immunotherapeutic approaches to pancreas cancer deserve further exploration.

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PURPOSE: Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults, and radiation is one of the main treatment modalities. However, cure rates remain low despite best available therapies. Immunotherapy is a promising modality that could work synergistically with radiation, which has been shown to increase antigen presentation and promote a proinflammatory tumor microenvironment. Programmed-death-1 (PD-1) is a surface receptor expressed on activated and exhausted T cells, which mediate T cell inhibition upon binding with its ligand PD-L1, expressed on many tumor types including human GBMs. We tested the combination of anti-PD-1 immunotherapy with stereotactic radiosurgery in a mouse orthotopic GBM model. METHODS AND MATERIALS: We performed intracranial implantation of mouse glioma cell line GL261 transfected with luciferase into C57BL/6 mice. Mice were stratified into 4 treatment groups: (1) control; (2) radiation only; (3) anti-PD-1 antibody only; and (4) radiation plus anti-PD-1 antibody. Overall survival was quantified. The mice were killed on day 21 after implantation to assess immunologic parameters in the brain/tumor, cervical lymph nodes, and spleen. RESULTS: Improved survival was demonstrated with combination anti-PD-1 therapy plus radiation compared with either modality alone: median survival was 25 days in the control arm, 27 days in the anti-PD-1 antibody arm, 28 days in the radiation arm, and 53 days in the radiation plus anti-PD-1 therapy arm (P<.05 by log-rank Mantle-Cox). Long-term survival was seen only in the combined treatment arm, with a fraction (15%-40%) of animals alive at day 180+ after treatment. Immunologic data on day 21 after implantation showed increased tumor infiltration by cytotoxic T cells (CD8+/interferon-gamma+/tumor necrosis factor-alpha+) and decreased regulatory T cells (CD4+/FOXP3) in the combined treatment group compared with the single modality arms. CONCLUSIONS: The combination of PD-1 blockade and localized radiation therapy results in long-term survival in mice with orthotopic brain tumors. These studies provide strong preclinical evidence to support combination trials in patients with GBM.

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APPENDIX A: Durvalumab Dose Calculations

Durvalumab Dosing

The durvalumab dosing should be done depending on subject weight (if subject is < 30kg)):

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle only needed for greater than 10% change in weight.

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10 (mL/vial)

Example:

1. Cohort dose: 20 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 600mg / 50 (mg/mL) = 12.0 mL

5. The theoretical number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

APPENDIX B

Schedule of study procedures: follow-up for subjects who have completed durvalumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progression of disease

Evaluation	**Time Since Last Dose of durvalumab**							
	Day (±3)	**Months (±1 week)**						**12 Months and Every 6 Months (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
ECOG performance status	X	X	X					
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status (phone call or email)	X	X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[b]	X							
CA 19-9	X							
Blood for correlative studies	X							
Blood for Future Biomedical Research	X							
Patient questionnaire (patient reported outcomes)[c] and health resource use	X		X					
Tumor assessment (CT)	Every 2 months							

[a] Full physical exam
[b] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
[c] For patient questionnaires different approaches based on indication and study design

APPENDIX C

Schedule of study procedures: follow-up for subjects who have discontinued durvalumab treatment due to confirmed progression of disease at the discretion of the investigator

Evaluation	**Time Since Last Dose of durvalumab**							
	Day (±3)	**Months (±1 week)**						**12 Months and Every 6 Months (±2 weeks)**
	30	**2**	**3**	**4**	**6**	**8**	**10**	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status[b]	X	X	X					
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status (phone call or email)	X	X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[c]	X							
CA 19-9	X							
Blood for correlative studies	X							
Blood for Future Biomedical Research	X							
Patient questionnaire (patient reported outcomes)[d] and health resource use	X							

[a] Full physical exam

[b] PS to be collected if available at the 2 monthly calls to obtain subsequent anti-cancer therapy and survival status

[c] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[d] For patient questionnaires different approaches based on indication and study design