Investigational Drug	Durvalumab (MEDI4736)
Substance(s)	Azacitidine/Decitabine (ASTX727)
Study Number	15-11430
Version Number	13.0
Date	09/20/2024

A Phase Ib Rescue Study With Oral Decitabine (ASTX727) and Durvalumab (MEDI4736) Combination Therapy in Recurrent and/or Metastatic SCCHN Subjects Who Have Progressed on Anti-PD-1, Anti-PD-L1, and/or Anti-CTLA-4 Therapy

IND Sponsor: Sara I. Pai, MD, PhD

SCHEDULE OF STUDY ASSESSMENTS

Schedule of study assessments: Screening and Treatment Period (13 months: maximum of 13 doses, last infusion week 48, last dose week 46)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	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	**-28 to -1***	**1**	**Day 1 of the week**			
Week	**-4 to -1**	**0**	**2, 4, 6, 8, 10, 12, etc.**	**4, 8, 12, 16, 20, etc.**	**8, 16, 24, 32, 40, 48**	**12, 24, 36, 48**
			(±5 days)		**(±7 days)**	
Written informed consent/assignment of subject identification number	X					
Demography and history of tobacco and alcohol use	X					
Previous treatments for head and neck cancer	X					
Inclusion/Exclusion criteria	X					
Medical[a] and surgical history	X					
Urine hCG or serum βhCG[b]	X	X		X		
Durvalumab (MEDI4736) administration				X [t, u]		
Tremelimumab administration				X[c, t, u]		
Oral decitabine (ASTX 727) or Azacitidine		X[d]		X[d, u]		
Physical examination[e]	X	X		X		

Schedule of study assessments: Screening and Treatment Period (13 months: maximum of 13 doses, last infusion week 48, last dose week 46)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	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	**-28 to -1***	**1**	**Day 1 of the week**			
Week	**-4 to -1**	**0**	**2, 4, 6, 8, 10, 12, etc.**	**4, 8, 12, 16, 20, etc.**	**8, 16, 24, 32, 40, 48**	**12, 24, 36, 48**
			(±5 days)		**(±7 days)**	
Vital signs (pre-, during and post-infusion vital signs assessments) [f]	X	X		X		
Weight	X	X		X		
Electrocardiogram[g]	X	X then as clinically indicated				
Adverse event/serious adverse event assessment	X[h]	X	All visits			
Concomitant medications	X	X	All visits			
Palliative radiotherapy	As clinically indicated					
ECOG performance status	X	X		X		
Liver enzyme panel[i]	X	X		X		
Serum chemistry (complete clin. chem. panel including liver enzymes) [i]	X	X		X		
Thyroid function tests (TSH and fT3 and fT4) [j]	X	X		X		
Hematology[i]	X	X		X		

Schedule of study assessments: Screening and Treatment Period (13 months: maximum of 13 doses, last infusion week 48, last dose week 46)

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	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	**-28 to -1***	**1**	**Day 1 of the week**			
Week	**-4 to -1**	**0**	**2, 4, 6, 8, 10, 12, etc.**	**4, 8, 12, 16, 20, etc.**	**8, 16, 24, 32, 40, 48**	**12, 24, 36, 48**
			(±5 days)		**(±7 days)**	
Urinalysis[l]	X	X		X		
Coagulation parameters[m]	X	As clinically indicted				
Stool sample collection	X				X[n]	
Collection of whole blood PBMCs for flow cytometry and circulating soluble factors (cytokines, chemokines, antibodies against tumor and self-antigens in circulation)		X			X[o]	
Tumor biopsy sample	X[p]				X[q]	
Tumour assessment (CT or MRI) and survival update[r]	X				X	
Bone scan(s)	X[s]					

*Within 28 days prior to study registration.

[a] Detailed hepatitis medical history for all subjects

[b] Pre-menopausal female subjects of childbearing potential only. Pregnancy test must be done within 72 hours prior to the first administration of IP and prior to dosing on Day 1 of every cycle. If the serum screening pregnancy test is performed >72 hours before first dose, a urine pregnancy test or a repeat serum pregnancy test should be performed. The subject may not receive IP until the Investigator has verified that the result of the pregnancy test is negative.

[c] For 4 cycles only for those patients receiving azacitidine.

[d] Refer to Sections 3.1, 6.2, and Table 1 for detailed dose-escalation schedule

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

[f] Subjects will have their blood pressure and pulse measured before, during, and after each 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 (ie, 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 follow the principles as described above or more frequently if clinically indicated.

[g] 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.

[h] For history of AEs/SAEs reported during prescreening additional information such as prior immunotherapy, medical history and concomitant medications may be needed.

[i] If screening laboratory assessments are performed within 3 days prior to Day 1 of protocol treatment 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.

[j] 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.

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

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

[n] Sample to be collected on Day 1 of Week 8 (+/- 7 days)

[o] The peripheral blood for flow cytometry will be obtained at the time of the tumor biopsy. Please refer to [q]

[p] Archival FFPE sample or fresh tissue wil be submitted for the screening or pre-dose Cycle Day 1 timepoint. HPV testing will be performed if indicated based on an oropharyngeal or unknown primary if HPV testing has not been previously done.

[q] A biopsy will be obtained on week 8 for the phase 1b portion of the study

[r] Timing of CT scans and survival update: default is every 8 weeks for the first 48 weeks and then every 12 weeks until confirmed PD, start of a new anticancer treatment, or withdrawal of consent. Tumor assessments are to be done up to and including the assessment which shows first disease progression. If a patient discontinues protocol treatment due to reasons other than disease progression, tumor assessments should be performed until first disease progression until 24 months from study registration. All patients including those who discontinue protocol therapy early, will be followed for response until first disease progression and survival until 24 months from study registration.

[s] Bone scans will be repeated only if symptomatic or with known bone metastasis, per standard of care

[t] For patients receiving azacitidine, the durvalumab and tremelimumab will start Day 1 Week 4 (Cycle 2). For patients receiving decitabine, the durvalumab will start Day 1 Week 4 (Cycle 2).

[u] In Cycle 1, subjects will receive azacitidine or decitabine only. For those patients receiving azacitidine, starting in Cycle 2, patients will continue with azacitidine, durvalumab, and tremelimumab combination therapy for Cycles 3-5 and and azacitidine and durvalumab for Cycles 6-12. For those patients receiving decitabine, starting in Cycle 2, patients will continue with decatibine and durvalumab combination therapy for Cycles 3-12.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report

Abbreviation or special term	Explanation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

Abbreviation or special term	Explanation
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival

Abbreviation or special term	Explanation
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
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care

Abbreviation or special term	Explanation
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1.1 Head and Neck Squamous Cell Carcinoma Background

Head and neck cancer is a collective term that encompasses the malignant tumors arising out of the oral cavity, pharynx, and larynx. Worldwide, over half a million new head and neck cancer cases are diagnosed each year, accounting for approximately 5% of all incident cancers. Over 90% of these head and neck cancers are squamous cell carcinoma subtype (SCCHN). SCCHN diagnosed at a localized stage (Stage I/II) can be effectively treated with single-modality treatment (either surgery or radiation), and the 5-year survival rate in these cases is over 80%. However, about 70% of SCCHN patients are diagnosed with a locally advanced or metastatic disease, where the survival rates are poor (Siegel et al 2014). Patients with locally advanced disease typically receive a multi-modality treatment with curative intent, usually involving varied combinations of surgical resection, radiation therapy, and chemotherapy. Most of these patients, however, eventually relapse with either locoregional recurrence, metastatic disease (20% to 30% of patients), or both (Vermorken and Specenier 2010).

First-line palliative treatment options for patients with locally recurrent (without salvage surgical or radiation option) and/or metastatic SCCHN include supportive care in conjunction with systemic therapy. Most regimens involve platinum compounds (cisplatin and carboplatin), either as single agents or in combination with other agents. Other most widely used agents include taxanes (docetaxel and paclitaxel), methotrexate, 5-fluorouracil, and cetuximab. After failure of first-line chemotherapy, objective responses to second-line cytotoxic chemotherapy are uncommon. Additionally, these regimens are associated with greater toxicity, and there is no evidence that second line treatment prolongs survival. The only approved targeted therapy for these second-line patients is Erbitux® (cetuximab), which has shown an objective response rate (ORR) of approximately 13% in patients who have failed first-line palliative therapy (Vermorken et al 2007).

Patients with recurrent or metastatic disease have a poor prognosis, with ORRs of approximately 20% to 35% and overall survival (OS) of 7 to 10 months observed with platinum-based chemotherapy and cetuximab regimens (Vermorken et al 2008). The management of patients with later stage disease is even more challenging, with currently available therapies providing ORRs of approximately 4% with methotrexate to 13% with cetuximab and OS of approximately 6 months (Shin and Khuri 2013, Vermorken et al 2008). In addition to poor response and survival outcomes, many palliative treatments may cause substantial toxicity. In summary, SCCHN represents a population with a large unmet need for new treatment options in the palliative setting (American Cancer Society 2012).

1.1.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs et al 2009). This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]). Biologically, SCCHN has attributes that suggest susceptibility to immune checkpoint blockade. Multiple lines of evidence suggest that SCCHN tumors create a highly immunosuppressive environment and that the PD-1/PD-L1 axis and inhibition of the activation of T cells play an important role in many cancers, including SCCHN, and may be amenable to therapeutic intervention with immune-modulating agents (Badoual et al 2010, Badoual et al 2013, Lyford-Pike et al 2013). Virally driven tumors, including human papillomavirus (HPV)-associated SCCHN, express viral antigens that may be recognized by the immune system. In HPV-associated cancers, the E6 and E7 tumor-specific antigens are known to be immunogenic, and studies have shown that HPV-specific T cell responses form upon vaccination with these proteins (Kaufmann et al 2002). Administering an immunotherapeutic agent to patients with HPV-positive SCCHN may result in an anti-tumor immune response versus HPV tumor-specific antigens. In patients with HPV-negative SCCHN, the driving etiology is thought to be tobacco use. Data suggest that cancers associated with smoking such as non-small-cell lung cancer (NSCLC), small-cell lung cancer, and SCCHN may carry a high mutational burden (Alexandrov et al 2013, Vogelstein et al 2013). Tumors with high mutational burden produce neoantigens, which may generate T-cell immunity. This hypothesis may explain the observation that patients with NSCLC with a history of heavy smoking may be more prone to respond to anti-PD-1 or anti-PD-L1 therapy as compared to light or never smokers. Specifically, higher ORRs following treatment with an anti-PD-L1 monoclonal antibody (mAb) were observed in patients with NSCLC with a history of smoking as compared to those without a history of smoking (Champiat et al 2014). These data suggest that application of immune-modulating therapies in SCCHN may have a positive impact on clinical outcomes.

1.1.3 Durvalumab (MEDI4736)

The non-clinical and clinical experience is fully described in the current version of the durvalumab (MEDI4736) Investigator's Brochure (IB Version 15.0).

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned

subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab (MEDI4736) is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab (MEDI4736) is interference of the interaction of PD-L1.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (Mu et al 2011). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity (Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008).

Durvalumab (MEDI4736) has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of the DCO dates (15Apr2015 to 18Sep2015, durvalumab (MEDI4736) IB version 9.0), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab (MEDI4736) clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received durvalumab (MEDI4736) monotherapy, 454 received durvalumab (MEDI4736) in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab (MEDI4736)-1108 following treatment with durvalumab (MEDI4736) 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 (MEDI4736) 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 (MEDI4736) ≥ 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 (MEDI4736) 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

As of 09Feb2015, 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.

1.1.4 Tremelimumab

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator's Brochure (IB Version 10.0).

Tremelimumab is an IgG 2 kappa isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also known as CD152 (cluster of differentiation 152). This is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the tremelimumab IB, Edition 6.0, for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cutoff dates (1 November 2015 for monotherapy studies and 15 April 2015 to 12 July 2015 for combination therapy studies), 34 sponsored clinical studies have been conducted as part of the tremelimumab clinical development programme. Of these, 13 studies have completed and 21 are ongoing. Eight tremelimumab monotherapy studies have been completed and 3 are ongoing. As of the data cutoff date of 1 November 2015, 973 patients received tremelimumab in completed monotherapy studies and the ongoing Study D4881C00024 and 569 patients have been treated in the ongoing blinded Phase IIb monotherapy Study D4880C00003 [DETERMINE]). In the

3rd ongoing monotherapy study (D4884C00001), no patients have been treated as of the data cutoff. In addition, approximately 59 patients have been treated with tremelimumab in monotherapy arms of combination studies. Five studies of tremelimumab in combination with other anticancer agents have been completed and 18 are ongoing. In total, 250 patients with a variety of tumour types have received tremelimumab in combination with other anticancer agents in these studies. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.4.2.2. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.6 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab.

1.1.5 Durvalumab (MEDI4736) in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012) because the mechanisms of action of CTLA-4 and PD-1 are non-redundant; therefore, AstraZeneca is also investigating the use of durvalumab (MEDI4736) + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumor activity of durvalumab (MEDI4736) + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab (MEDI4736) every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

Study D4190C00006: As of 20Feb2015, durvalumab (MEDI4736) PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts (1a, 2a, 3a, 3b, 4, 4a, 5, 5a, 8, and 9) following durvalumab (MEDI4736) every 4 weeks (Q4W) or Q2W dosing in combination with tremelimumab Q4W regimens. An approximately dose-proportional increase in PK exposure (C_{max} and area under the concentration-time curve from 0 to 28 days [AUC_{0-28}]) of both durvalumab (MEDI4736) and tremelimumab was observed over the dose range of 3 to 15 mg/kg durvalumab (MEDI4736) Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. It is to be noted that steady state PK parameters are based on limited numbers of subjects. The observed PK exposures of durvalumab (MEDI4736) and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of 20Feb2015, ADA data were available from 60 subjects for durvalumab (MEDI4736) and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti-durvalumab (MEDI4736) antibodies post treatment. One of 53 subjects was ADA positive for anti-tremelimumab antibodies post treatment. There was no clear relationship between ADA and the dose of either durvalumab (MEDI4736) or tremelimumab, and no obvious association between ADA and safety or efficacy.

Durvalumab (MEDI4736) has also been combined with other anticancer agents, including gefitinib, dabrafenib, and trametinib. To date, no PK interaction has been observed between durvalumab (MEDI4736) and these agents.

1.1.6 Azacitidine/Oral Decitabine (ASTX727)

Hypomethylating agents (HMAs), such as decitabine and azacitidine, are effective treatment modalities for hematologic cancers and are FDA-approved for higher risk myelodysplastic syndromes (MDS). HMAs have also shown promising clinical activity in acute myeloid leukemia (AML). Consecutive daily dosing for a minimum of 5 or 7 days in 28-day cycles is the labelled schedule and is necessary to achieve the desired effects, particularly in higher risk patients. Reduction in the number of days of treatment per cycle have been studied, but have not been pursued for marketing approval with health authorities (Jabbour et al 2017; Garcia-Manero et al 2013). Continued monthly treatment for patients who respond is now the standard of care to avoid early relapse (Cabrero et al 2015). Treatment, ie, 5 to 7 daily visits for a 1-hour intravenous (IV) infusion or a large-volume subcutaneous injection continuing for several months or even years, represents a significant hardship for patients. A possible consequence is non-compliance or earlier discontinuation of a beneficial treatment. More convenient oral administration of HMAs has proven difficult due to rapid metabolism by cytidine deaminase (CDA) during passage through the gastrointestinal (GI) mucosa and liver. To achieve even modest exposures of drug requires administration of large doses, which are associated with Grades 3 and 4 gastrointestinal toxicity (nausea, vomiting, and diarrhea) and high variability in systemic exposures (Garcia-Manero et al 2011). Successful development of an oral HMA will ease the burden of long-duration parenteral therapy, particularly for those patients who are benefitting the most and need continuing treatment for long periods.

Astex Pharmaceuticals is developing a drug product composed of the new chemical entity (NCE) cedaxuridine (E7727), a CDA inihibitor (Ferraris et al 2014); and decitabine, both to be administered orally. Because cedaxuridine inhibits CDA in the gut and liver, the ASTX727 fixed-dose combination (FDC) facilitates oral administration of decitbaine, achieving exposure and hypomethylation activity similar to IV decitabine at the currently approved dosing schedule of 20 mg/m2 daily x 5 days. Key intrapatient pharmacokinetic (PK) comparison and safety data from the Phase 1-2 trial of ASTX727 (ASTX727-01) have enabled justification of a Phase 3

trial designed to confirm exposure similar to IV decitabine. Decitabine was approved in 2006 by the United States Food and Drug Administration (US FDA) as Dacogen® (decitabine, DAC) (Dacogen US Package Insert [PI] 2019), administered as a 1-hour IV infusion for the treatment of higher risk patients with MDS and chronic myelomonocytic leukemia (CMML) and approved by the European Medicines Agency (EMA) in 2012 (Dacogen Summary of Product Characetristics 2019) for the treatment of treatment-naïve adult AML patients who are not candidates for intensive chemotherapy.

Azacitidine (AZA), an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and DNA synthesis and metabolism, and causes cytotoxicity. Since the early 1970s, azacitidine has been investigated in the United States (US) for the treatment of acute leukemia. Clinical trials have focused primarily on patients with disease refractory to conventional chemotherapy. These investigations indicated azacitidine has activity in the treatment of acute myeloid leukemia (AML). Clinical trials from the 1980's through recent years have been conducted to evaluate the effects of azacitidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (thalassemia and sickle cell anemia), and myelodysplastic syndromes (MDS) as well as the use of Azacitidine in the treatment of AML in elderly patients.

Vidaza® (azacitidine injection) is approved by the US Food and Drug Administration (FDA) for 5 subtypes of the French-American British (FAB) classification system of myelodysplastic syndrome (MDS). Vidaza® is also approved by the European Commission for the treatment of adult MDS, acute myeloid leukemia (AML) and chronic myeolomonocytic leukemia (CMMoL) patients who are not eligible for hematopoietic stem cell transplantation. Vidaza® can be administered by intravenous (IV) or subcutaneous (SC) routes as designated by country approval.

After its incorporation into a cell's DNA during the S-phase of the cell cycle, AZA forms covalent adducts with DNA Methyltransferase 1 (DNMT1) and depletes this enzyme required for the maintenance of DNA methylation patterns, thereby altering the epigenetic status of the cell. Epigenetic changes are covalent modifications of chromatin (DNA and histone proteins) that mediate the stable transmission of a gene's transcriptional status through cell division. One of the first recognized epigenetic alterations in cancer was DNA methylation. The addition of a methyl group to cytosine in the dinucleotide (CpG) is catalyzed by DNA methyltransferases (DNMTs) and is associated with transcriptional repression of genes with high density of CpGs (CpG islands) in the vicinity of their promoters (Miranda, 2007). Genomic methylation patterns are precisely regulated during normal embryonic development and differentiation and have been found to be altered in specific ways in cancer. Specifically, cancer cell genomes are typified by reduced methylation globally with focal areas of aberrant hypermethylation in the CpG islands of genes encoding known tumor suppressors such as PTEN and BRCA1 as well as genes encoding proteins required for apoptosis, including caspase 8, DAPK and Apaf-1. DNA methylation-based silencing can thus contribute to the establishment and maintenance of the transformed state and limit the effectiveness of anticancer therapies.

1.1.7 DNA Methyltrasnferase Inhibitor Experience in Solid Tumors

Both azacitidine and 2'-deoxy-5-azacitidine prevent DNA methylation, and they also have direct cytotoxic effects as a result of incorporation into DNA and RNA. Single-agent 2'-deoxy-5-azacitidine has demonstrated good antitumor activity in nude mice with SCCHN xenografts (Braakhuis et al, 1988). A number of phase II studies using single-agent azacitidine or 2'-deoxy-5-azacitidine have been performed in solid tumors with disappointing results, including breast, gastrointestinal, lung, kidney, testicular, melanoma, sarcoma, and lymphomas (Santini et al, 2001; Weiss et al, 1977). The doses of azacitidine or 2'-deoxy-5-azacitidine used in these trials were near the MTD, rather than the optimal biologically effective dose (Aparicio et al, 2002). Therefore, single-agent therapeutic responses were disappointing and patients experienced side effects that were probably related more to the inherent toxicity of aza-nucleoside inhibitors than to their demethylating activity. It has been shown in cancer cells exposed to DNA demethylating agent, demethylation of genes can occur at drug concentrations that are substantially lower than those required for a cytotoxic effect (Bender et al, 1998). Additionally, genes demethylated can be remethylated within a few days (Velicescu et al, 2002).

Treatment schedules for DNA hypomethylation agents have been modified to include multiple courses of treatment to sustain demethylation and reduced drug concentrations to decrease the severity of side effects. This has been shown to be maximized for biologic effects and minimized for toxicity. In studies conducted in patients with MDS, administration of azacitidine has been modified to daily low-dose treatment (75-100 mg/m^2), seven out of 28 days, and appeared to have been well tolerated, with increased response rates (Silverman et al, 2002).

Chan et al. have conducted a study using daily 3-hour intravenous infusion of azacitidine at a dose of 75 mg/m^2/d for 7 days (5 days for HIV infected patient) in 10 patients with Epstein-Barr virus-associated tumors (8 with nasopharyngeal carcinoma, 1 with Hodgkin's lymphoma, and 1 with AIDS-associated lymphoma) (Chan et al, 2004). Tumor biopsy specimens were obtained within 72 hours of the conclusion of the last infusion of the first cycle of therapy, and compared to pretreatment specimens. They have found substantial degrees of demethylation were detected in all latent and lytic Epstein-Barr virus promoters examined, even in patients only receiving 5-day treatment. They concluded that pharmacologic reversal of dense CpG methylation in tumor tissue can be achieved after 5 to 7 days of intravenous azacitidine treatment at the same dose used in MDS.

Given the unimpressive clinical activity of single-agent azacitidine or 2'-deoxy-5-azacitidine against various types of solid tumor malignancy, it is likely that combination therapy with other anticancer agents will be required to achieve meaningful clinical response.

A Phase 1/II study of combined epigenetic therapy with azacitidine and entinostat, inhibitors of DNA methylation and histone deacetylation, respectively, in extensively pretreated patients with recurrent/metastatic non-small cell lung carcinoma was performed (Juergens et al, 2011). Ten patients participated in the phase I portion of the study; three patients received 30 mg/m2/d

azacitidine and seven received 40 mg/m2/d azacitidine. Entinonstat was administered to all patients at a fixed dose of 7 mg on days 3 and 10 of each cycle. In total, 42 patients, including the seven patients from the phase I portion, were treated at the phase II azacitidine dose of 40 mg/m2. None of the 3 patients in the 30 mg/m2 azacitidine cohort experienced DLTs. One patient in the 40 mg/m2 azacitidine cohort withdrew from the study due to decreasing performance status and was replaced. None of the remaining 6 phase I patients had DLTs. The recommended phase II dose was therefore defined as 40 mg/m2 azacitidine given on days 1-6 and 8-10 plus 7 mg of entinostat given on days 3 and 10 of each 28-day cycle. All patients experienced at least 1 treatment-related adverse event. The most common treatment-related, non-hematologic adverse events included low-grade skin/injection-site reactions (93%), fatigue (71%), nausea (73%), vomiting (40%), constipation (36%), anorexia (29%), electrolyte disturbances (29%), and hyperglycemia (22%). These adverse events are anticipated toxicities of either azacitidine or entinostat and generally required no intervention except anti-emetics and other agents for gastrointestinal side effects, which were easily medically managed. Anemia was the most common hematologic toxicity (40%) and lymphopenia and thrombocytopenia were seen in 27% of patients. Grade 3 or 4 toxicites were seen in 28% of patients during cycle 1. The most common grade 3 or 4 toxicity was fatigue. Grade 3 or 4 hematologic toxicities were transient and generally asymptomatic. Four patients with anemia all improved following a one-time red blood cell transfusion. There were no correlations between the worst grade of toxicity and azacitidine or entinostat exposure ($p>0.05$). One patient had a complete response that lasted 14 months. A second patient had a partial response that lasted 8 months. Ten patients had stabilization of disease of at least 12 weeks. One of these patients had stable disease for 18 months and another for 14 months, both with prolonged symptomatic improvement. The maimal dose planned in the phase I dose escalation was 40 mg/m2/d in an effort to remain at an epigenetically targeted dose rather than a directly cytotoxic dose.

Phase II studies of 2'-deoxy-5-azacitidine and cisplatin combination using a concurrent administration schedule (daily on day 1-3 of a 21 day cycle) have been conducted in patients with metastatic non-small cell lung cancer and advanced squamous cell carcinoma of the cervix. In cervical cancer patients, this combination produced moderate activity as a first-line treatment, achieving 38.1% partial response, 23.8% stable disease, and 19-week median survival. The hematological toxicity was rather significant with grades III/IV neutropenia in 68.0% of cases, and one out of 25 patients died of complications caused by drug-related neutropenic sepsis (60). In non-small cell lung cancer patients, this combination did not show significant activity, only achieving 3 minor responses in 14 patients and 15-week median survival, and more than 50% of grade III/IV neutropenia toxicity was noted (Schwartsmann et al, 2000). The possible explanations for the shortcomings in these studies include the use of MTD not the biologically effective dose of 2'-deoxy-5-azacitidine without validation of DNA hypomethylation effect, and administration of 2'-deoxy-5-azacitidine concurrently with cisplatin.

In 2008, Bast et al. reported on a phase IIa study of a sequential regimen administering azacitidine 75 mg/m2/day for 5 days plus carboplatin AUC 5 on day 2 once every 28 days in patients with platinum resistant or refractory ovarian cancer (Bast et al, 2008). There were 29 evaluable patients with 1 complete response, 3 partial response (response rate: 14%) and 10

stable disease. The median duration of response was 7.5 months. Overall survival at one-year was 53%. Patients classified as having platinum-resistant disease had an objective response of 22% and one-year overall survival of 67%, compared to 0% and 33% in platinum-refractory patients, respectively. Side effects were tolerable, including neutropenia (3% grade 4), thrombocytopenia (3% grade 4), anemia, fatigue, nausea, and pain/irritation at the injection sites. This study highlights the ability of a hypomethylating agent to reverse platinum resistance which is the target population of our proposed study.

In order to utilize the period of demethylation of drug-resistance and/or pro-apoptotic genes as a window of epigenetic sensitization for combination therapies, it has been shown in cell culture and animal studies that DNA hypomethylation agents need to be given several days before chemotherapeutic agents to achieve optimal synergistic effect (Plumb et al, 2000; Soengas et al, 2001). Importantly, the timing of drug administration appears to be associated with therapeutic response. If DNA hypomethylation agents are given at the same time or after the cytotoxic drug is administered, sensitization is lost. Therefore, it is recommended in clinical combination trials with DNA hypomethylation agents, the administration of the cytotoxic drug should be delayed for several days to achieve the highest possible demethylation of tumor DNA (Lyko et al, 2005). *This study provides the rationale for administering one cycle of the hypomethylating agent prior to the immunotherapy.*

1.1.8 DNA Methyltransferase Inhibitors in Head and Neck Cancer

Limited data exists with DNA methyltransferase inhibitors in head and neck cancer. A non-randomized, open label, dose escalation phase I study of azacitidine and cisplatin was conducted in advanced head and neck cancer patients. Azacitidine was administered as a subcutaneous injection daily from day 1 to day 5 and cisplatin was given at 75 mg/m2 IV on day 8 on a 28-day cycle. Four patients received azacitidine 37 mg/m2 daily from day 1 to day 5 and two patients were treated with azacitidine 60 mg/m2 daily from day 1 to day 5. No patient had dose-limiting toxicities. Four patients completed at least 2 cycles of treatment and were evaluated for clinical response by CT scan and DNA methylation effect. One partial response was noted in a patient eith metastatic tongue squamous cell carcinoma after 2 cycles of treatment with 37 mg/m2/d. This patient received a total of 3 cycles of treatment and achieved progression free survival for 15 months. Another patient with recurrent salivary gland carcinoma had stable disease after 2 cyclces of treatment at a dose of 60 mg/m2/d. There was inhibition of global DNA methylation after azacitidine treatment in all four treated patients. This study was not completed due to poor patient accrual; however, the preliminary results are intriguing and demonstrate global DNA methylation effect at doses as low as 37 mg/m2/day when administered from day 1 to day 5 (Liao et al, 2012).

1.2 Research Hypothesis

The hypothesis of this study is that both azacitidine, durvalumab (MEDI4736), and tremelimumab combination therapy or oral decitabine (ASTX727) and durvalumab (MEDI4736) combination theraoy are safe and will result in a clinically meaningful PFS based on RECIST 1.1. It is hypothesized that SCCHN patients who fail immune checkpoint blockade

monotherapy (such as anti-PD-1, anti-PD-L1, anti-CTLA-4, and/or others) have a paucity of cytotoxic CD8+ T cells within the tumor microenvironment. Tumor antigens and major histocompatibility complex (MHC) Class I/II molecules are epigenetically silenced in solid cancers, including SCCHN, and tumor antigen presentation can be enhanced with hypomethylating agents, such as azacitidine or decitabine, leading to immune-mediated antitumor effects when combined with immune checkpoint blocking antibodies.

1.3 Rationale for conducting this study

Patients with recurrent and/or metastatic SCCHN who have progressed during or after treatment with a platinum-containing regimen for recurrent and/or metastatic disease have a poor prognosis with limited standard-of-care therapeutic options, which only have transient and limited benefit (ORR: 4% to 13%, progression-free survival [PFS]: 2.5 months, and OS: 5.5 months) (Shin and Khuri 2013, Vermorken et al 2008). Thus, there is a significant unmet medical need for additional treatment options for use in this patient population.

Durvalumab (MEDI4736), an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012, Topalian et al 2012). In addition, although clinical experience with durvalumab (MEDI4736) is limited, currently available data from Study 1108 indicates encouraging response rates (RRs) and duration of response (DoR) with a manageable safety profile in patients with a variety of solid malignancies, including patients with SCCHN treated with durvalumab (MEDI4736) as monotherapy.

Tremelimumab, an anti-CTLA-4 targeting agent that blocks the interaction with CD80 and CD86, may help prolong and enhance T-cell activation and expansion. This hypothesis is supported by emerging clinical data from both tremelimumab studies (Kirkwood et al 2010, Ribas et al 2013) and studies with a related anti-CTLA-4 antibody, ipilimumab. However, data for tremelimumab monotherapy in SCCHN are not available.

The rationale for evaluating the combination of durvalumab (MEDI4736) and tremelimumab is supported both by preclinical and clinical data, including safety and tolerability data. Mouse models of transplantable solid tumors using surrogate antimouse antibodies show superior antitumor activity of combination therapy as compared to monotherapy. Furthermore, the CTLA-4 and PD-1/PD-L1 pathways are non-redundant, suggesting that targeting both may have additive or synergistic activity. Lastly, the combination of CTLA-4 and PD-1 blockades in melanoma has been shown to result in higher ORRs and 1-year survival compared to either agent alone (Wolchok et al 2013). Similar results have been observed in an ongoing study of durvalumab (MEDI4736) + tremelimumab in NSCLC, with further updated details presented in this clinical study protocol.

Based on the preliminary clinical efficacy and safety data observed in patients with solid tumors, including advanced SCCHN, in Study 1108 with durvalumab (MEDI4736) monotherapy, and

in patients with NSCLC in Study D4190C00006 with durvalumab (MEDI4736) and tremelimumab, there is an ongoing phase II study which will determine the activities of durvalumab (MEDI4736) and tremelimumab as a combination therapy in SCCHN patients, as well as the efficacy of durvalumab (MEDI4736) and tremelimumab combination therapy versus durvalumab (MEDI4736) or tremelimumab monotherapy. The preliminary efficacy, safety, and tolerability data of the durvalumab (MEDI4736) and tremelimumab combination in Study D4190C00006 support the development of this combination in SCCHN.

Since patients who progress on immune checkpoint blockade are hypothesized to have a paucity of CD8+ T cells, we are not only interested in establishing the role of durvalumab (MEDI4736) in combination with tremelimumab but also with other investigational agents and therapies which will enhance the CD8+ T cell frequency and improve upon current ORR of 15-27% with pembrolizumab monotherapy and a ORR of 11% with durvalumab (MEDI4736) monotherapy in locally recurrent and/or metastatic SCCHN patients (Seiwert et al and Segal et al, ASCO 2015; Cohen EE et al, ESMO 2017). It is hypothesized that the addition of azacitidine or oral decitabine will lead to an increased frequency of CD8+ T cells and, thus, when combined with durvalumab (MEDI4736) and tremelimumab will result in an improved PFS and ORR in subjects with SCCHN. A potential way to improve PFS and ORR may be with epigenetic therapy through the reactivation of the host immune response through the hypomethylation of silenced genes (Kenney, 2014). This is supported in the scientific literature for SCCHN.

There is frequent wide-spread methylation of cancer-related genes in SCCHN (Colacino JA et al, 2013).

A subset of SCCHNs are associated with HPV infection and have documented HPV DNA methylation which is associated with silencing of HPV immunodominant antigens (Park et al, 2011).

Viral lytic reactivation via demethylation may provide a path to targeting viral-associated SCCHN.

Azacitidine induces demethylation of the viral genome in SCCHN (Chan, 2004).

DNA methylation inhibitors can reverse chemoresistance and prevent the development of acquired drug resistance (Zhang, 2012b).

Promoter hypermethylation is a major mechanism for inactivation of critical tumor suppressor genes (*p16,*RASSF1A) (Lo, 2013).

Based on the current scientific literature, there is strong rationale for evaluating the combination of azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), and tremelimumab in SCCHN patients.

1.3.1 Durvalumab (MEDI4736) + tremelimumab combination therapy dose rationale

The durvalumab (MEDI4736) + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab (MEDI4736) and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

In order to reduce the dosing frequency of durvalumab (MEDI4736) to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg durvalumab (MEDI4736) q4w. PK simulations from the durvalumab (MEDI4736) monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w durvalumab (MEDI4736). The observed durvalumab (MEDI4736) PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab (MEDI4736) 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when durvalumab (MEDI4736) and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median C_{max} at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab (MEDI4736) monotherapy. There was evidence of augmented PDx activity relative to durvalumab (MEDI4736) monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg durvalumab (MEDI4736) plus 1 mg/kg tremelimumab combinations.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab and 10 mg/kg durvallumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab (MEDI4736) + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab (MEDI4736). As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab (MEDI4736) with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing

doses of durvalumab (MEDI4736) may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab (MEDI4736).

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥3 AEs or treatment-related SAEs. No dose-limiting toxicities were reported.

Preliminary clinical activity of the durvalumab (MEDI4736) and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab (MEDI4736) q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. All together, the data suggested that a 20 mg/kg durvalumab (MEDI4736) + 1 mg/kg tremelimumab dose combination should be selected for further development.

AstraZeneca performed a safety evaluation for subjects randomized to the durvalumab 1500 mg Q4W plus tremelimumab 300 mg x 1 dose regimen in study D4190C00022 (Part 2B, Arm D, and Part 3, Arm D) as part of the interim analysis. As of May 7, 2018, safety data in the form of Tables and Listings are available for 24 subjects: 10 Part 2B, Arm D subjects (6 subjects from Japan and 4 from the USA) and 14 subjects from Part 3, Arm D (4 from South Korea, 2 from Taiwan, 1 from Italy, 5 from USA and 2 from Singapore). These patients all completed at least 4-weeks of safety follow up.

Safety information for these subjects are summarized below (accurate as of 7 May 2018).

All 24 subjects treated in Arm D (of Parts 2B and 3) of the study experienced at least one adverse event (AE). These events were considered to be treatment-related in 21 (87.5%) subjects. Eleven (45.8%) subjects reported at least one event of Grade ≥ 3 severity with the events being considered treatment-related in 7 subjects (29.2%).

One Grade 5 event of acute kidney failure (SOC: Renal and urinary disorders) was reported which was assessed as unrelated to study treatment. This subject received one cycle of treatment (durvalumab and tremelimumab combination). There were no treatment-related deaths observed as at the data cut-off of 7 May 2018.

Seven (29.2%) subjects experienced at least one serious adverse event (AE). These events were considered to be treatment-related in 2 (8.3%) subjects.

One subject (4.2%), subject 20015250002, experienced an event of hyperthyroidism (SOC: Endocrine disorders), which did not meet serious criteria, but was considered to be treatment related. This subject had received 2 cycles of treatment (one durvalumab and tremelimumab combination and one durvalumab monotherapy). The event of hyperthyroidism led to treatment discontinuation for this subject.

A total of 22 (91.7%) subjects experienced at least one Adverse Event of Special Interest (AESI). Twenty (83.3%) subjects experienced at least one AESI which was considered treatment related. Eleven (45.8%) subjects experienced at least one AESI which was of Grade ≥ 3 severity. Seven (29.2%) subjects experienced at least one AESI which was considered treatment related and of Grade ≥ 3 severity.

Observed treatment-emergent Adverse Events with Severity ≥ Grade 3 are detailed in Table 1.

Table 1 **Treatment-emergent Adverse Events with Severity ≥ Grade 3 by System Organ Class and Preferred Term**

System Organ Class (SOC) & Preferred Term	Part 2B (n=10)	Part 3 (n=14)	Total (n=24)
Subjects with at least one ≥ grade 3 event	**6 (60.0%)**	**5 (35.7%)**	**11 (45.8%)**
Cardiac disorders	1 (10.0%)	0	1 (4.2%)
Acute myocardial infarction	1 (10.0%)	0	1 (4.2%)
Atrial fibrillation	1 (10.0%)	0	1 (4.2%)
Cardiac failure congestive	1 (10.0%)	0	1 (4.2%)

Table 1 **Treatment-emergent Adverse Events with Severity ≥ Grade 3 by System Organ Class and Preferred Term**

System Organ Class (SOC) & Preferred Term	Part 2B (n=10)	Part 3 (n=14)	Total (n=24)
Gastrointestinal disorders	1 (10.0%)	2 (14.3%)	3 (12.5%)
Abdominal pain	0	1 (7.1%)	1 (4.2%)
Ascites	1 (10.0%)	0	1 (4.2%)
Pancreatitis	0	1 (7.1%)	1 (4.2%)
Hepatobiliary disorders	1 (10.0%)	0	1 (4.2%)
Hepatic function abnormal	1 (10.0%)	0	1 (4.2%)
Infections and infestations	2 (20.0%)	0	2 (8.3%)
Meningitis	1 (10.0%)	0	1 (4.2%)
Peritonitis bacterial	1 (10.0%)	0	1 (4.2%)
Investigations	5 (50.0%)	3 (21.4%)	8 (33.3%)
Alanine aminotransferase increased	1 (10.0%)	1 (7.1%)	2 (8.3%)
Amylase increased	2 (20.0%)	0	2 (8.3%)
Aspartate aminotransferase increased	3 (30.0%)	1 (7.1%)	4 (16.7%)
Blood alkaline phosphatase increased	0	1 (7.1%)	1 (4.2%)
Lipase increased	3 (30.0%)	2 (14.3%)	5 (20.8%)
Neutrophil count decreased	1 (10.0%)	0	1 (4.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (10.0%)	0	1 (4.2%)
Tumour associated fever	1 (10.0%)	0	1 (4.2%)
Renal and urinary disorders	0	1 (7.1%)	1 (4.2%)
Acute kidney injury	0	1 (7.1%)	1 (4.2%)
Skin and subcutaneous tissue disorders	3 (30.0%)	1 (7.1%)	4 (16.7%)
Eczema	1 (10.0%)	0	1 (4.2%)
Erythema multiforme	1 (10.0%)	0	1 (4.2%)
Rash	1 (10.0%)	0	1 (4.2%)
Rash generalised	1 (10.0%)	0	1 (4.2%)
Rash maculo-papular	0	1 (7.1%)	1 (4.2%)
Vascular disorders	1 (10.0%)	0	1 (4.2%)
Hypertension	1 (10.0%)	0	1 (4.2%)

Subjects with at least one serious and related adverse event are outlined in Table 2.

Table 2 Subjects with at Least One Serious Related Event

System Organ Class (SOC) & Preferred Term	Part 2B (n=10)	Part 3 (n=14)	Total (n=24)
Subjects with at Least One Serious Related Event	**1 (1.0%)**	**1 (7.1%)**	**2 (8.3%)**
Endocrine disorders	0	0	0
Adrenal insufficiency	0	0	0
Hypophysitis	0	0	0
Hypopituitarism	0	0	0
Gastrointestinal disorders	1 (10.0%)	1 (7.1%)	2 (8.3%)
Autoimmune pancreatitis	0	0	0
Colitis	0	0	0
Diarrhoea	1 (10.0%)	0	1 (4.2%)
Vomiting	0	1 (7.1%)	1 (4.2%)
Infections and infestations	0	0	0
Clostridium difficile colitis	0	0	0
Encephalitis	0	0	0
Metabolism and nutrition disorders	1 (10.0%)	1 (7.1%)	2 (8.3%)
Decreased appetite	0	0	0
Dehydration	1 (10.0%)	1 (7.1%)	2 (8.3%)
Diabetic ketoacidosis	0	0	0
Hyperglycaemia	0	0	0
Other (System organ class with only one PT)	0	0	0
Fatigue	0	1 (7.1%)	1 (4.2%)
Hepatic function abnormal	0	0	0
Tumour rupture	0	0	0
Hepatic encephalopathy	0	0	0

Adverse Events of Special Interest (AESI), based on Investigator selection, and noted in this patient population are detailed in Table 3.

Table 3 Adverse Events of Special Interest (Investigator Selection)

Event	Part 2B (n=10)	Part 3 (n=14)	Total (n=24)
Subjects with at least one event of special interest	**8 (80.0%)**	**14 (100.0%)**	**22 (9.2%)**
Dermatitis	8 (80.0%)	9 (64.3%)	17 (70.8%)
Select hepatic events	5 (50.0%)	4 (28.6%)	9 (37.5%)
Diarrhoea	3 (30.0%)	2 (14.3%)	5 (20.8%)
Pancreatitis	4 (40.0%)	5 (35.7%)	9 (37.5%)
Hyperthyroidism	1 (10.0%)	2 (14.3%)	3 (12.5%)
Hypothyroidism	1 (10.0%)	0	1 (4.2%)
Nephritis/Acute Renal Failure	0	1 (7.1%)	1 (4.2%)
Hypophysitis	0	0	0
Colitis	0	0	0
Adrenal insufficiency	0	0	0
Infusion related/ Hypersensitivity/ Anaphy	0	0	0

Overall, the safety data remain consistent with the observed toxicity profile for the standard dosing regimen of 1500 mg Q4W durvalumab and 75 mg Q4W x 4 doses tremelimumab. The observed safety data is also consistent with PK modelling predictions which were performed to compare 300 mg tremelimumab single dose with tremelimumab 75 mg Q4W for 4 doses (standard dose). This PK modelling predicted that the same cumulative AUC tremelimumab exposure would be expected for both dose regimens and thus a similar safety profile could be anticipated.

1.3.2 Rationale for 4 cycles of combination therapy followed by durvalumab (MEDI4736) monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Schadendorf et al 2013).

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for

melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (Hodi et al 2014, Brahmer et al 2014, Drake et al 2013). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis (Topalian et al 2014).

MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (Herbst et al 2013, Wolchok et al 2013).

Similar long-term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as durvalumab (MEDI4736), or the combination of the two.

1.3.3 Rationale for study design

The safety and efficacy of oral decitabine (ASTX727) and durvalumab (MEDI4736) combination therapy are being evaluated in patients with recurrent or metastatic SCCHN who have progressed during or after treatment with a platinum-containing regimen for recurrent or metastatic disease.

1.4 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with oral decitabine (ASTX727) and durvalumab (MEDI4736) combination therapy, respectively, prior to the overall benefit:risk assessment.

1.4.1 Potential benefits

1.4.1.1 Durvalumab (MEDI4736)

The majority of the safety and efficacy data currently available for durvalumab (MEDI4736) are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. Overall, 456 of 694 subjects treated with durvalumab (MEDI4736) 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%). (Antonia et al 2014b).

1.4.1.2 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; Korn et al 2008) were observed (Kenney 2014

Kenney SC, Mertz JE. Regulation of the latent-lytic switch in Epstein-Barr virus. Semin Cancer Biol 2014;26:60-68. Available at: http://dx.doi.org/10.1016/j.semcancer.2014.01.002.

Kirkwood et al 2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant (Ribas et al 2013. Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.4.1.3 Durvalumab (MEDI4736) + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma (Wolchok et al 2013). Of the 102 subjects with advanced NSCLC treated with durvalumab (MEDI4736) in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan;

this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

Current experience with single-agent IMT studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate, for patient enrichment for IMTs. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor infiltrating cells may be associated with greater clinical benefit.

Data from ongoing studies with durvalumab (MEDI4736) and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (eg, NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious (in terms of ORR) in patients who are PD-L1-positive.

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1–positive tumors. There is also an unmet medical need in patients with PD-L1–negative tumors that needs to be addressed. Data, as of 27 January 2015 from Study 006 show that with the addition of tremelimumab to durvalumab (MEDI4736), the ORR can be increased to 25% in patients with PD-L1 negative NSCLC. As patients with PD-L1 positive disease can also have an increase in ORR, from 25% with durvalumab (MEDI4736) monotherapy, to 36% with the combination of durvalumab (MEDI4736) and tremelimumab, the study will enroll all patients with NSCLC, with an emphasis on those determined to be PD-L1 negative.

1.4.1.4 Azaciditine/Oral Decitabine (ASTX727)

Azacitidine can be administered by intravenous (IV) or SC routes. When azacitidine is given SC, it is rapidly absorbed, reaching a peak plasma concentration within 30 minutes. The bioavailability is 89% when administered via an IV route, and azacitidine is metabolized by the liver into six metabolites. It has a mean half-life of approximate 40 minutes for the parent compound and a mean elimination half-life of four hours for the parent drug and metabolites. Azacitidine and/or its metabolites are rapidly cleared by the kidneys. The effects of renal or hepatic impairment, gender, age, and race on the pharmacokinetics of azacitidine have not been studied (Marcucci et al, 2005).

The MTD of azacitidine following SC administration has not been determined, although SC doses as high as 100 mg/m^2 daily for 7 days every 28 days were administered in the MDS studies without reaching dose-limiting toxicities (Marcucci et al, 2005). In contrast, the MTD for IV administration of azacitidine was reported to be in the range of 150 to 200 mg/m^2/day when given daily for 5 days every 14 to 28 days, with the major toxicities being leukopenia, thrombocytopenia, nausea and vomiting in patients with leukemia, lymphoma, or colorectal cancer (von Hoff et al, 1976). The MTD IV dose was reported to be as high as 500 mg/m^2 when given once weekly or 150 mg/m^2 when given twice weekly to patients with solid tumors (Marcucci et al, 2005; Karon et al 1973). Our proposed dose of azaciditine is 40 mg/m2/d and 75 mg/m2/d administered via SC injection which is much lower than the dose administered in other clinical trials.

Clinical efficacy of ASTX727 is consistent with efficacy described for IV decitabine in MDS patients. At the therapeutic dose of 100 mg cedazuridine and 35 mg decitabine (administered concomitantly as separate capsules or as the FDC tablet), the overall Phase 2 results from Study ASTX727-01 showed complete response (CR) rate of 21. 3%, with hematologic improvement in an additional 16.3% of subjects. In subjects who were transfusion-dependent at baseline, ASTX727 was associated with 50% transfusion-independence.

Study ASTX727-02 is a multicenter, randomized, crossover study of the ASTX727 FDC tablet (100 mg cedazuridine + 35 mg decitabine) in subjects with MDS/CMML or AML subjects with a primary endpoint of AUC equivalence with IV decitabine. Enrollment of MDS/CMML subjects for the primary PK analysis was completed in late 2018, with 124 subjects treated with ASTX727 as of 25 January 2019. Enrollment (including enrollment of AML subjects) is continuing with a target enrollment of approximately 200 subjects.

1.4.2 Potential risks

1.4.2.1 Durvalumab (MEDI4736)

Potential risks, based on the mechanism of action of durvalumab (MEDI4736) and related molecules, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease.

Study CD-ON-durvalumab (MEDI4736)**-1108:** The safety profile of durvalumab (MEDI4736) monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab (MEDI4736)-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab (MEDI4736) 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 07May2015, among the 694 subjects treated with durvalumab (MEDI4736) 10 mg/kg Q2W in Study CD-ON-durvalumab (MEDI4736)-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 (MEDI4736) 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 (MEDI4736) were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab (MEDI4736) monotherapy in Study CD-ON-durvalumab (MEDI4736)-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 (MEDI4736) 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 (MEDI4736) 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 (MEDI4736). 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 (MEDI4736). Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab (MEDI4736) treatment due to AEs. Events that led to discontinuation of durvalumab (MEDI4736) 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.

1.4.2.2 Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with

melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014 and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product (IP), and deaths.

1.4.2.3 Durvalumab (MEDI4736) + tremelimumab

No safety studies in animals have been performed combining tremelimumab with durvalumab (MEDI4736). As both CTLA-4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. Durvalumab (MEDI4736) and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

Study D4190C00006: The safety profile of durvalumab (MEDI4736) and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with durvalumab (MEDI4736) and tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the durvalumab (MEDI4736) 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported

SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjects). Additional safety results from this study are presented in Section 1.3.1 and the durvalumab (MEDI4736) IB.

In the literature (Wolchok et al 2013), using the combination of the same class of drugs (eg, anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

1.4.2.4 Fixed Dosing for durvalumab (MEDI4736) and tremelimumab

A population PK model was developed for durvalumab (MEDI4736) 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 (MEDI4736) (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab (MEDI4736) 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.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (*N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma*) [Wang et al. 2014]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75

mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab (MEDI4736), simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others [Ng et al 2006, Wang et al. 2009, Zhang et al, 2012,Narwal 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 . 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 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 750 mg Q2W MEDI4736 (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (MEDI4736) (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Fixed dosing of durvalumab (MEDI4736) and tremelimumab are recommended only for subjects with > 30kg body weight due to endotoxin exposure.

1.4.2.5 Azacitidine/Oral Decitabine (ASTX727)

Results from safety pharmacology studies with cedazuridine do not highlight an off-target concern for cardiovascular, respiratory, or other organ systems (see Section 4.1.3 for more details). The cumulative data from in vitro and in vivo safety pharmacology studies indicate that cedazuridine does not show CV effects. Cedazuridine had negligible inhibition of hERG current up to 300 µM (100422.FJT) and did not have an effect on heart rate, blood pressure, ECG, or respiratory parameters in conscious telemetered male monkeys administered cedazuridine up to 200 mg/kg (20123940). In addition, cardiovascular assessments included as part of a 4-cycle GLP toxicity study in cynomolgus monkeys showed no abnormalities in ECG parameters following dosing with cedazuridine up to 200 mg/kg/day for 7 consecutive days (28-day cycles) (20124863).

The toxicology program for ASTX727 has focused on cedazuridine as a single agent, as the toxicities of decitabine administered as a 5-day dosing regimen are well understood due to

extensive clinical experience (although toxicology studies are being conducted to assess toxicity of decitabine with more extended dosing regimens). Administration of cedazuridine for 7 days resulted in a NOAEL of 1000 mg/kg/day in CD-1 mice and 200 mg/kg/day in rhesus monkeys (the highest doses tested in each species) (Table 17). In longer term studies (approximately 3 months) in which cedazuridine was administered daily for 7 days in 28-day cycles, the NOAEL was 300 mg/kg in male mice, 100 mg/kg in female mice, and 60 mg/kg in cynomolgus monkeys. Target organs for toxicity in mice were microscopic changes in lymph nodes, bone marrow, and testes and ovaries, and changes in hematology parameters. In monkeys, cedazuridine affected hematology parameters and mucosal epithelial cells of the GI tract; these findings were not deemed severely toxic, thus the highest non-severely toxic dose (HNSTD) in monkeys was 200 mg/kg.

The clinical dose of 100 mg cedazuridine in humans offers an approximately 40-fold margin based on dose comparison and using the HNSTD from monkeys converted to the human equivalent dose (HED). Continuous dosing of cedazuridine for 28 days in mice showed similar toxicology effects to the 7-day cyclic dosing with a NOAEL of 300 mg/kg and effects on lymphoid tissues and testes. In a combination one-cycle study with limited toxicity evaluation of cedazuridine and decitabine in monkeys, findings were limited to reversible reductions in hematology parameters, dose-related increased in bone marrow M:E ratio in males but not in females, and possible test article-related hepato-celluar centriolobular vacuolation in 1 female. At the clinically relevant dose of oral decitabine (2 mg/kg, HED of approximately 24 mg/m2) co-administration with cedazuridine at up to 6 mg/kg produced decitabine systemic exposures approximately 4.7- to 4.9-fold higher than reported in the clinic for IV decitabine (20 mg/m2 1-hour infusion).

Cedazuridine was found to be mutagenic but only at the highest concentration tested (Ames test) and genotoxic (chromosomal aberrations test) at concentrations that were also cytotoxic, but was negative in the in vivo mouse micronucleus test at doses up to 2000 mg/kg. Carcinogenicity studies have not been conducted.

Toxicokinetic exposures in mice and monkeys showed no meaningful accumulation of cedazuridine on Day 7 vs Day 1, or on Day 63 vs Day 1. Based on cedazuridine systemic exposures seen after a 100 mg dose in humans, toxicokinetic exposure margins achieved in monkeys (combined male plus female) after the HNSTD of 200 mg/kg (3-month GLP) were approximately 28-fold. Exposure margins in mice at the NOAEL dose (3-month GLP study) were approximately 22-fold in females (after NOAEL of 100 mg/kg) and 54-fold in males (NOAEL 300 mg/kg).

Additional toxicology information is provided in Section 4.3 in the IBv6.

Refer to to the Dacogen US PI (2019) and for additional nonclinical information regarding decitabine.

At this stage of development, no new clinically significant safety issues have been identified for ASTX727 that are inconsistent with the safety profile of IV decitabine. (Refer to Dacogen US PI 2019.)

Results from clinical trials and other studies demonstrate that the most common toxicities associated with azacitidine are gastrointestinal (nausea, vomiting, diarrhea, constipation, anorexia), constitutional (fatigue, fever, rigors), musculoskeletal and connective tissue (arthralgia, pain in limb, weakness), pulmonary (cough, dyspnea), skin or soft tissue (injection site bruising from SC injection, rash, erythema), and hematologic (neutropenia, anemia, leukopenia). Nausea, vomiting and diarrhea are among the most common adverse effects of azacitidine and appear to be self-limiting with repeated cycles of therapy. Myelosuppression also occurs in a majority of patients, and accounts for the most common reason of dose reduction and treatment termination during clinical trials. Infrequent adverse effects include neuromuscular aches, generalized weakness, renal tubular acidosis, and liver enzyme abnormalities. Erythema and burning at the injection site can occur following SC administration, which usually resolves within 24-72 hours.

1.4.3 Overall benefit-risk and ethical assessment

There remains a significant unmet medical need for additional treatment options for patients with recurrent and/or metastatic SCCHN who have progressed during or after treatment with a platinum-containing regimen for recurrent or metastatic disease. Treatment with agents targeting PD-1/PD-L1 or CTLA-4 has shown activity in several tumor types, in a subset of patients deriving meaningful and durable benefit. Duravalumab has shown clinical activity in patients with recurrent or metastatic SCCHN as a single agent. In addition, preliminary data generated with durvalumab (MEDI4736) + tremelimumab combination therapy in patients with NSCLC have shown promising activity with objective, durable responses. Thus, these agents may potentially offer benefit to this patient population. The study design aims to minimize potential risks, and intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the investigational products (IPs). The toxicity profile of the combination durvalumab (MEDI4736) + tremelimumab includes fatigue, colitis, diarrhea, AST or ALT increases, amylase and lipase increases, rash and pruritus and other immune-mediated reactions, which were mostly reversible and manageable by the available protocol treatment guidelines.

In the literature (Wolchok et al 2013), using the combination of the same class of drugs (eg, anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of treatment-related AEs in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea

(34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with grade 3 or 4 treatment-related events in 53%. The most frequent of these grade 3 or 4 treatment related events include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). SAEs related to the treatment were noted in 49% of patients. Frequent grade 3 or 4 selected AEs related to the combination therapy included hepatic events (in 15% of patients), gastrointestinal (GI) events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

No safety studies in animals have been performed combining tremelimumab with durvalumab (MEDI4736) or with azacitidine in combination with tremelimumab and durvalumab (MEDI4736). As both CTLA 4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. Durvalumab (MEDI4736) and tremelimumab, either alone or in combination did not induce cytokine release in blood from any donor.

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypotheses under evaluation, the durvalumab (MEDI4736) + tremelimumab treatment proposed for evaluation in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby improving QoL and potentially extending survival. Patients with recurrent/metastatic SCCHN who have failed a prior line of therapy have a dismal prognosis with median survival of less than 6 months. Agents targeting the PD-1/PD-L1 pathway have shown promising activity in patients with recurrent/metastatic SCCHN. Although the patients who may be more likely to benefit from therapies with PD-1/PD-L1 targeting agents are those whose cancers express PD-L1 in the tumor microenvironment (see **Section 1.2.4**), an unmet need remains for patients with PD-L1 negative tumors despite the potential impact of immunotherapy. Preclinical and clinical evidence indicate that combination of PD-1/PD-L1 and CTLA4 targeting agents may provide synergistic antitumor activity, regardless of PD-L1 expression levels (Wolchok et al 2013). Therefore, the investigation of the potential therapeutic efficacy of durvalumab (MEDI4736) + tremelimumab combination in patients with recurrent/metastatic disease with PD-L1–negative tumors is acceptable, and the overall benefit/risk assessment is reasonable per the proposed study design.

2. STUDY OBJECTIVE

2.1.1 Primary objective(s)

To determine the Biologically Effective Dose (BED) of oral decitabine (ASTX727) in combination with durvalumab (MEDI4736) therapy.

2.1.2 Secondary Objective:

To assess the safety of oral decitabine (ASTX727) in combination with durvalumab (MEDI4736) therapy.

3. STUDY DESIGN

3.1 Overview of study design

This is a non-randomized, open-label, Phase Ib study to assess the safety and efficacy of oral decitabine (ASTX727) and durvalumab (MEDI4736) combination therapy in the treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) who have progressed during or after treatment with anti-PD-1, anti-PD-L1, and/or anti-CTLA-4 for recurrent and/or metastatic disease. The primary endpoint is to determine the BED of oral decitabine (ASTX727) in combination with durvalumab (MEDI4736) therapy. The secondary endpoint is to assess the safety of oral decitabine (ASTX727) in combination with durvalumab (MEDI4736) therapy.

The trial opened with the use of subcutaneous (SC) injection of azacitidine. All patients received azacitidine SC injection on either Days 1-5 alone or Days 1-5 and 8-12 in a 4-week cycle, durvalumab (MEDI4736) 1500 mg via intravenous (IV) infusion every 4 weeks (q4w), and tremelimumab 75 mg via IV infusion q4w. Azacitidine was administered alone in Cycle 1 and the combination of azacitidine, durvalumab, and tremelimumab therapy was started in Cycle 2. Dose Limiting Toxicity (DLT) was assessed through 28 days post Cycle 2. After cycle 2, patients continued with azacitidine, durvalumab and tremelimumab combination therapy for Cycles 3-5 and azacitidine and durvalumab for Cycles 6-12 or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met, whichever occured first. However, treatment consisting of 5 to 10 daily visits for a large-volume SC injection continuing for several months or even years, represented a significant hardship for patients with possible consequences of non-compliance or earlier discontinuation of a beneficial treatment. Therefore, an oral DNA methyltransferase inhibitor is being evaluated to ease the burden of daily visits for those patients who are benefitting the most and need continuing treatment for long periods. Furthermore, since the oral DNA methyltransferase inhibitor is investigational, we plan to combine it with the FDA approved durvalumab.

Therefore, all patients enrolled with or after protocol version 11.0 will receive an oral tablet of ASTX727 (35 mg decitabine/100 mg cedazuridine) daily on either Days 1-3, Days 1-4, or Days 1-5 and durvalumab (MEDI4736) 1500 mg via IV infusion x 1 in a 4-week cycle. Oral

decatibine (ASTX727) will be administered alone in Cycle 1 and the combination of oral decatibine (ASTX727) and durvalumab therapy will be administered in Cycles 2-12 or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met, whichever occurs first. The BED will be assessed on pre-treatment and post-treatment biopsies obtained at week 8. BED is defined as the dose of oral decatibine (ASTX727) that results in at least a 10% decrease in LINE-1 methylation from the baseline biopsy sample to the 8-week on-treatment tumor biopsy sample in at least 50% of patients treated within the same dose level. Accrual will be suspended until review of the LINE-1 methylation level in tissue from baseline and 8 weeks post baseline has been completed from patients entered into the first 2 dose levels (oral decitabine on Days 1-3 alone and Days 1-4 in a 4-week cycle). If the BED has not been determined in the first 2 dose levels and it is safe to do so, then the study will re-open to accrual and a subsequent group of 3 patients will receive the 3rd dose level. If both the first 2 dose levels result in $\geq$ 10% decrease in LINE-1 methylation, then the dose which induces the greatest fold change in HLA Class I/II APM expression and/or CD8+ T cell infiltration and with the lowest AE profile will be the dose utilized for the dose expansion group. Once the BED is determined, dose escalation will stop and the BED will be used in the expansion cohort. Dose Limiting Toxicity (DLT) will be assessed through 28 days post Cycle 2.

Although assessment of the BED is primary, the dose also needs to be safe. Each dose will be assessed for safety according to a stopping rule and a DLT toxicity definition as outlined in the protocol and statistical section. Subjects will be sequentially assigned to the cohorts. The first 6 enrolled subjects will receive one tablet daily on Days 1-3 of a 28-day cycle. If two or more of the first six subjects experience a DLT, then the dose will be reduced and an additional six patients will be treated at the reduced dose. If two or more of the six at the reduced dose experience a DLT, then the study will be terminated. If at any time during accrual to a cohort, 2 or more patients in a cohort experience DLT, enrollment to that cohort will be terminated. If less than two of the six patients treated at dose level 1 experience a DLT, a subsequent group of six patients will receive dose level 2.

Subjects cannot change groups or dose assignments upon the initiation of the study protocol.

Tumor assessments will be performed using CT or MRI. Efficacy and survival for all patients will be assessed by objective tumor assessments every 8 weeks (q8w) +/- 7 days for the first 48 weeks (relative to the date of the first infusion) then q12w in patients who have disease control after 12 months until confirmed objective disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Categorization of objective tumor response assessment will be based on RECIST 1.1: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective tumor response (CR or PR) will be confirmed at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed. All scans showing PD should be confirmed at the next scheduled

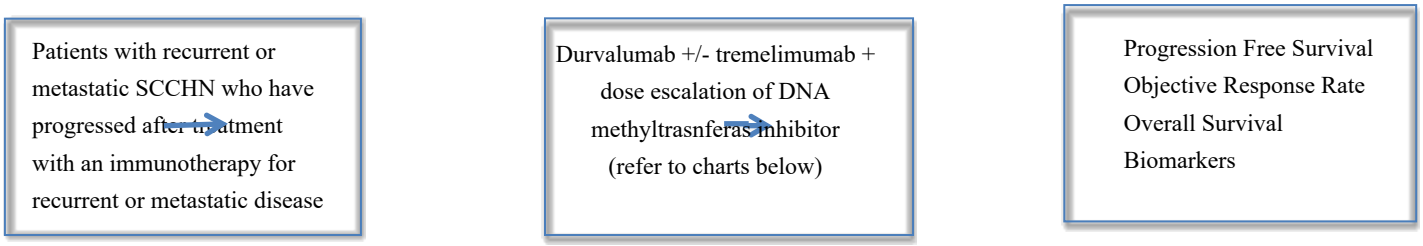
visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with IP should continue between the initial assessment of progression and its confirmation. If progression is not confirmed, then the patient should continue receiving study treatment and participate in study assessments.

Patients who achieve and maintain disease control (ie, CR, PR, or SD) through the end of the 12-month treatment period will enter follow-up. When these patients experience evidence of PD, with or without confirmation, during follow-up and meet the criteria for treatment in the setting of PD, they will be given the option to restart their assigned IP treatment for up to an additional 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Patients should have a baseline tumor assessment within 28 days of restarting treatment with their assigned IP; all further scans should occur q8w (relative to the date of restarting treatment) until study treatment is stopped (maximum of 12 months of further treatment). Only patients whom the Investigators determine do not have any significant, unacceptable, or irreversible toxicities and would continue to receive benefit from therapy can restart a second 12 months of retreatment upon PD. Patients with confirmed progression with azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), and/or tremelimumab combination therapy cannot continue therapy or obtain retreatment if the progression occurred during dosing and after confirmed response in the target lesions (ie, the response and progression events both occurred while receiving active IP during the same treatment period in the target lesions).

Following completion or discontinuation of treatment, patients will enter a follow-up period.

3.2 Study schema

Figure 1. Study Flow Chart



Cohort (# of pts)	Azacitidine (28-day cycle)	Grade 3 or higher	2-fold DNMT1 inhibition in ≥50% of patients
D-1 (6)	20 mg/m2 on Days 1-5	MTD[2]	BED[3]
1 (6)	40 mg/m2 on Days 1-5	MTD[2]	BED[3]

2 (6)	40 mg/m2 on Days 1-5 and 8-12	MTD[2]	BED[3]
3 (6)	75 mg/m2 on Days 1-5	MTD[2]	BED[3]

[1]Azacitidine will be given starting Cycle 1 and durvalumab and tremelimumab will be given starting Cycle 2
[2]MTD (maximally tolerated dose)
[3]BED (biologically effective dose)

Cohort (# of pts)	**Oral Decitabine (ASTX727) (28-day cycle)**	**Grade 3 or higher**	**10% decrease in LINE-1 methylation in ≥50% of patients**
BD-1 (6)	ASTX727 one tablet on Days 1-2	MTD[2]	BED[3]
B1 (6)	ASTX727 one tablet on Days 1-3	MTD[2]	BED[3]
B2 (6)	ASTX727 one tablet on Days 1-4	MTD[2]	BED[3]
B3 (6)	ASTX727 one tablet on Days 1-5	MTD[2]	BED[3]

[1]Oral decitabine (ASTX727) will be given starting Cycle 1 and durvalumab will be given starting Cycle 2
[2]MTD (maximally tolerated dose)
[3]BED (biologically effective dose)

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (**Section 4.1**) and none of the exclusion criteria (**Section 4.2**) for this study.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill 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 or adult male or female (according to age of majority as defined as ≥18 years)

3. Histologically confirmed recurrent or metastatic SCCHN (oral cavity, oropharynx, hypopharynx, larynx, or unknown primary) not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Patients who refuse radical resection are eligible.

4. Tumor progression or recurrence during or after treatment with anti-PD1, anti-PDL1, anti-PDL2, anti-CTLA4, and/or other combination of immunotherapy.

5. Must give valid written consent to provide archival FFPE and/or newly acquired tumor tissue for the purpose of establishing baseline PD-L1 status as well as consent to provide on- and/or post-treatment tumor biopsy sample.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrollment

7. Life expectancy of $\geq$ 6 months

8. At least 1 lesion that can be accurately measured at baseline as $\geq$ 10 mm in the longest diameter (except lymph nodes which must have a short axis $\geq$15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

9. Adequate normal organ and marrow function as defined below (within 28 days prior to study registration):

   - Hemoglobin $\geq$ 8.0 g/dL
   - Absolute neutrophil count (ANC) $\geq$ 1.0 x 10^9/L ($\geq$ 1500 per mm^3)
   - Platelet count $\geq$ 100 x 10^9/L ($\geq$100,000 per mm^3)
   - Serum bilirubin $\leq$ 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) $\leq$ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be $\leq$ 5x ULN

- Serum creatinine level ≤1.5 x ULN and 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:

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

Females:

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

10. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

11. Male subjects with a female partner of childbearing potential must commit to true abstinence from heterosexual contact or commit to the use of male condom plus spermicide throughout the course of the study, and avoid fathering a child during the course of the study (including dose interruptions) and for 6 months following the last dose of azacitidine.

12. All men and women of childbearing potential must use acceptable methods of birth control throughout the study as described below:

Females of childbearing potential: Recommendation is for at least one highly effective contraceptive methods during the study and must agree to continue using such precautions for 180 days after the last dose of investigational product.

Non-sterilized males : Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 180 days after the last dose of investigational product.

13. 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.

Inclusion criteria for genetics research study (optional)

For inclusion in the optional (DNA) genetics research study, patients must fulfill the following criteria:

1. Provide informed consent for genetic sampling and analyses.

2. If a patient declines to participate in genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

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 AstraZeneca staff and/or staff at the study site)

2. Histologically confirmed squamous cell carcinoma of any other primary anatomic location in the head and neck (eg. paranasal cavity) and non-squamous histologies (eg. nasopharynx or salivary gland)

3. History of another primary malignancy except for:

   - Malignancy treated with curative intent and with no known active disease ≥5 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 eg, cervical cancer in situ

4. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 21days prior to the first dose of study drug

5. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab (MEDI4736) or tremelimumab, 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

6. Any unresolved toxicity NCI CTCAE grade 2 from previous anti-cancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

    - Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis and may be included after consultation with the Study Physician.

    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with their assigned IP (eg, hearing loss) may be included after consultation with the Study Physician.

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

8. Abnormal coagulation parameters (PT >15 secondss, PTT>40 seconds, and/or INR >1.5)

9. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, psoriasis, diabetes, hypothyroidism, and/or other autoimmune disease that is readily managed with treatment and not at risk for serious exacerbation on study treatment are not excluded.

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

11. History of primary immunodeficiency

12. History of allogeneic organ transplant

13. History of hypersensitivity to durvalumab (MEDI4736), tremelimumab, or any excipient

14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, myocardial infarction in the past 6 months, active peptic ulcer disease or gastritis, active bleeding diatheses including 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

15. Known history of previous clinical diagnosis of tuberculosis

16. Uncontrolled systemic fungal, bacterial or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment)

17. History of leptomeningeal carcinomatosis

18. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab (MEDI4736) or tremelimumab

19. 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

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

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

22. Subjects with uncontrolled seizures.

23. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of azacitidine, durvalumab (MEDI4736) and/or tremelimumab therapy. Lactating females must agree not to breast feed throughout this period.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of study treatment

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 10.3.

6. Dose-limiting toxicity (See Section 5.5 for definition of DLT)

7. Grade ≥ 3 infusion reaction

8. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits

9. Initiation of alternative anticancer therapy including another investigational agent

10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with azacitidine, durvalumab (MEDI4736), and tremelimumab

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 10.0 and Appendix 1 or 2, 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 patients including those who discontinue protocol therapy early, will be followed for response until first disease progression and survival until 24 months from study registration. 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 3 months as an alternative.

Withdrawal of consent

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

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab (MEDI4736) and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab **(MEDI4736)** and tremelimumab to the investigator as a solution for infusion after dilution.

5.1.1 Formulation/packaging/storage

Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 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 (MEDI4736) must be used within the individually assigned expiry date on the label.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg or 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. The nominal fill volume is 20 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure. Tremelimumab must be used within the individually assigned expiry date on the label.

5.1.2 Treatment regimens

Durvalumab (MEDI4736) + **tremelimumab combination therapy**

For patients receiving azacitidine, patients will receive 1500 mg durvalumab (MEDI4736) via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycle or 300 mg tremelimumab via IV infusion x1, and then continue 1500 mg durvalumab (MEDI4736) q4w starting on Week 16 or Week 8 for up to 8 months. For patients receiving decitabine, patients will receive 1500 mg durvalumab (MEDI4736) via IV infusion q4w starting on Week 4 for up to 12 months. Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab (MEDI4736) infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration

will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab (MEDI4736) and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab (MEDI4736) and tremelimumab infusion).

5.1.3 Duration of treatment and criteria for retreatment

Retreatment is allowed (once only) for patients meeting the retreatment criteria below. The same treatment guidelines followed during the initial 12-month treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients receiving the combination of durvalumab (MEDI4736) and tremelimumab may undergo retreatment in 2 clinical scenarios, described below:

1. Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart treatment with the combination upon evidence of PD, with or without confirmation according to RECIST 1.1, during follow-up.

2. Patients who complete the 4 dosing cycles of the combination of durvalumab (MEDI4736) and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab (MEDI4736) monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

3. Before restarting their assigned treatment, the Investigator should ensure that the patient:

4. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient

5. Still fulfils the eligibility criteria for this study, including re-consenting to restart durvalumab (MEDI4736) and tremelimumab

6. Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation.

7. Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial

12 months of treatment (relative to the date of randomization) until study treatment is stopped (maximum of 12 months of further treatment).

During the retreatment period, patients receiving azacitidine, durvalumab (MEDI4736) + tremelimumab may resume durvalumab (MEDI4736) dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 doses each and continue durvalumab (MEDI4736) monotherapy at 1500 mg q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy (a total of 9 additional doses). For those patients receiving decitabine and durvalumab (MEDI4736), the patient may resume durvalumab (MEDI4736) dosing at 1500 mg q4w beginning at Week 4 (a total of 12 additional doses).

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. A patient with a confirmed progression receiving durvalumab (MEDI4736) + tremelimumab cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy (q4w dosing) and progression occurs in a target lesion that has previously shown a confirmed response.

Patients who the Investigator determines may not continue treatment will enter follow-up.

5.1.4 Study drug preparation of durvalumab (MEDI4736) and tremelimumab

Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (MEDI4736) (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) or 300 mg x 1 tremelimumab (equivalent to 1 mg/kg total) is included in the current study.

Preparation of durvalumab (MEDI4736) **doses for administration with an IV bag**

The dose of durvalumab (MEDI4736) 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 (MEDI4736) 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 (MEDI4736) and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab (MEDI4736) for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% dextrose, with a final durvalumab (MEDI4736) 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 30.0 mL of IV solution from the IV bag prior to addition of durvalumab (MEDI4736). Next, 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab (MEDI4736)) 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 unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

Durvalumab (MEDI4736) 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 (MEDI4736), the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (+10/-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 (MEDI4736) **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 in the table, a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab 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 tremelimumab 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

It is recommended that the prepared final IV bag be stored in the dark at 2ºC-8°C (36°F-46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of either 75 mg tremelimumab or 300 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. To prepare a 75 mg dose, remove 3.75 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.75 mL of tremelimumab (ie, 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. To prepare the 300 mg dose, remove 15 ml of IV solution from the IV bag prior to addition of tremelimumab. Next, mL of tremelimumab (ie, 300 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 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 unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

Tremelimumab 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

tremelimumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (+10/-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 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.

Tremelimuab 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 in the table, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

5.1.5 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

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 and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, 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.

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 patients to an intensive care unit if necessary

5.1.6 Accountability and dispensation

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

5.1.7 Disposition of unused investigational study drug

The investigator is responsible for keeping accurate records of the clinical supplies received from Astrazeneca/MedImmune and ASTX Pharmaceuticals, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.
Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. Certificates of delivery and destruction must be signed.

5.2 Azacitidine/Oral Decitabine (ASTX727)

Azacitidine, Vidaza®, has the following chemical structure:

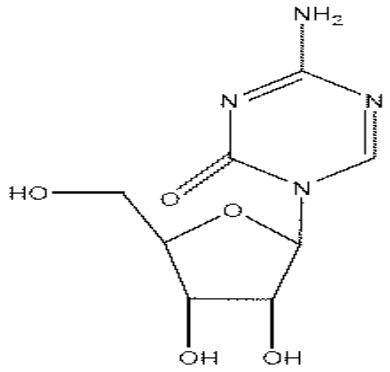


Figure 2a. Chemical Structure of Azacitidine

Azacitidine is (4-amino-1-β-D-ribofuranosyl-s-triazin-2(1*H*)-one). The empirical formula is $C_8H_{12}N_4O_5$. The molecular weight is 244 amu.

ASTX727 is under development as an FDC tablet for oral administration of cedazuridine (E7727) (100 mg), a novel cytidine deaminase inhibitor (CDAi), and decitabine (35 mg), an FDA-approved HMA for IV infusion (**Figure 2b and Figure 2c**). The CDAi cedazuridine enables the oral bioavailability of decitabine.

Figure 2b. Molecular Structure of Cedazuridine

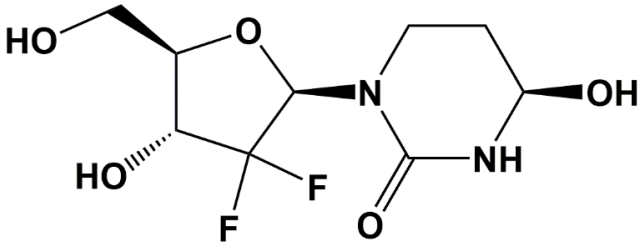
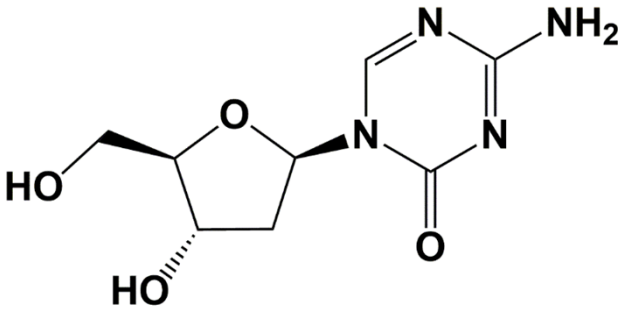


Figure 2c. Molecular Structure of Decitabine



Nomenclature and properties of the components of ASTX727 (cedazuridine and decitabine) are provided in Table 4.

Table 4: Nomenclature and Properties: Cedazuridine and Decitabine

	Cedazuridine	**Decitabine**
Compendial Name	cedazuridine	decitabine
Chemical Name (IUPAC)	(4*R*)-1-[(2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-4-hydroxy-1,3-diazinan-2-one	4-amino-1-[(2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2(1*H*)-one
(CAS) Registry Number	1141397-80-9	2353-33-5
Chemical Formula	C9H14F2N2O5	C8H12N4O4
Molecular Weight	268.21 Daltons	228.21 Daltons

Pharmacologic Class	Cytidine deaminase inhibitor	Anatomical therapeutic chemical (ATC) code L01BC08, Antineoplastic and immunomodulating agents, pyrimidine analogues. Decitabine is a cytosine deoxynucleoside analogue that inhibits DNA methyltransferase.[a]
Solubility	Soluble in dimethylsulfoxide and 0.1 M HCl, sparingly soluble in water and pH 7.2 buffer, slightly soluble in methanol and ethanol, and insoluble in n-heptane, ethyl acetate, acetonitrile, 1-octanol, and methyl tert-butyl ether. Not hygroscopic.	Slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol, sparingly soluble in water and soluble in dimethylsulfoxide (DMSO).

[a] Source: Decitabine European Public Assessment Report (EPAR) accessed 09 April 2019. https://www.ema.europa.eu/en/documents/product-information/dacogen-epar-product-information_en.pdf

5.2.1 Formulation/packaging/preparation/storage

Azacitidine (Vidaza®) is supplied as a lyophilized powder in 100 mg single-use vial, and should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved**.** The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL.

Preparation for Immediate Administration:

Azacitidine doses should be drawn up into 1 to 4 syringes of equal volume per institutional guidelines. The product must be administered within 1 hour after reconstitution when stored at room temperature.

Preparation for Delayed Administration:

The reconstituted product may be kept in the vial or drawn into a syringe. The product must be refrigerated immediately, and may be held under refrigerated conditions (2ºC - 8ºC, 36ºF- 46ºF) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Reconstituted azacitidine may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2 and 8°C (36 and 46°F). The azacitidine vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. Do not save any unused portions for later administration.

Azacitidine is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling. Several guidelines on this subject have been published (ASHP,

2006; NIH, 1999; NIOSH, 2004; OSHA, 1999; Polovich, 2005). If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water. Procedures for proper handling and disposal of azacitidine should be applied according to standards established at each facility for cytotoxic drugs.

Prior to development of ASTX727 tablet (see below), cedazuridine and decitabine were administered separately in capsules.

The new ASTX727 tablet is a fixed-dose combination of 100 mg cedazuridine and 35 mg decitabine for oral administration. The drug product is a red, oval shaped film-coated, immediate-release tablet (Figure 3). The formulation excipients include lactose, hypromellose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and Opadry II 85F15458 Red. The Opadry is a tablet coating formula that contains titanium dioxide, polyvinyl alcohol, polyethylene glycol, talc, and iron oxide red. The clinical drug products are either plain faced on both sides, or have a debossed marking of "H35" on one side and plain faced on the other. This tablet was used in the Phase 3 trial.

Figure 3. ASTX727 Tablet

All drug products are packed in 5-count opaque high-density polyethylene (HDPE) bottle with a child resistant closure. Each bottle contains either 1 or 2 desiccant canisters for moisture absorption. The desiccant canisters should remain in the bottle at all times and must not be ingested. Tablets are to be stored on site as indicated in the study-specific Pharmacy Manual (provided by Astex). Tablets should be dispensed by the study pharmacist according to institutional policy and per study protocol, and at-home storage instructions should be given to the study subject.

5.2.2 Doses and treatment regimens

All subjects will be administered either a fixed dose and schedule of durvalumab (MEDI4736) and tremelimumab with azacitidine or a fixed dose and schedule of durvalumab (MEDI4736) with ASTZ727 The dose and schedule of azacitidine or decitabine will determined by the dose escalation schema (**Sections 3.2 and 6.2, Table 2**). For those patients receiving azacitidine, in Cycle 2, azacitidine will be administerd 60 minutes following the infusion of durvalumab. For subsequent cycles, azacitidine will be administered after the completion of the durvalumab infusion.

5.2.3 Dose administration

Subjects who enter screening will be assigned the next available subject number. All eligible subjects will receive oral decitabine (ASTX727) at the assigned dose. Subjects will complete a self administration drug diary (**Appendix 8**). The dose will be taken at the same time (+/-1 hour) for the first 5 days of each cycle. If the subject misses the dose and remembers before 6:00 PM that day, the subject may make-up the dose. If it is after 6:00PM, the subject should wait until the next scheduled dosing time (the next day) and take the next scheduled dose. If the dose is vomited, the patient should not re-dose. The tablets cannot be crushed, chewed, or dissolved in water. The drug should be taken with 8 fluid ounces of water. The drug should be taken in the fasted state (no food for at least 2 hours before and 2 hours after taking the dose). The bottles containing the tablets should be stored at room temperature.

5.2.4 Accountability and dispensation

Accurate recording of all IP administered will be made in the appropriate section of the subject's case report form (CRF) and source documents, including patient drug diaries (**Appendix 8**). The subject should bring the drug diary and any empty or partially empty bottles into the clinic for their scheduled visits. The Investigator or designee is accountable for the compliance of all study-specific IP either administered or in their custody during the course of the study.

5.2.5 Disposition of unused investigational study drug

Any unused investigational study drug will be returned to the Pharmacy for proper disposal in accordance with hospital policy of any unused chemotherapeutic agents.

6. TREATMENT PLAN

6.1 Subject enrollment

6.1.1 Assignment of screening number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

6.1.2 Procedures for randomization

This is not a randomized study. All eligible subjects will be allocated, by non-random assignment, to trial treatment and will receive a unique number. This unique number is termed a randomization number throughout the protocol for operational purposes. The randomization number identifies the subject for all procedures occurring after treatment allocation. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than one unique number. Treatment assignment will be done based on the schema described in **Sections 3.2 and 6.2, Table 2**. All patients will receive the same fixed dose of durvalumab (MEDI4736) and tremelimumab (based on a weight greater than 30 kg) and oral decitabine (ASTX727) will be dose escalated if safe to do so. Enrolled patients will be sequentially assigned to the cohorts. After the enrollment of 6 evaluable patients into the 1st group (eligible patients who at least begin protocol treatment and have an evaluable pre- and on-treatment (8-week) biopsy sample available), the next 6 patients will be enrolled into the 2nd cohort if safe to do so. After the enrollment of 6 evaluable patients into the 2nd cohort, the next 6 patients will be enrolled into the 3rd cohort only if the BED has not been determined, and the group in which the BED has been determined will be expanded to enroll 10 patients. Additional subjects may be enrolled into the cohort(s) to ensure that the required number of evaluable pre- and on-treatment biopsy samples are available to adequately determine the BED. Patients cannot change groups or dose assignments upon the initiation of the study protocol.

6.1.3 Procedures for handling subjects incorrectly enrolled

Subjects who fail to meet the eligibility criteria should not receive study medication. Subjects who are incorrectly enrolled but found to not meet all the eligibility criteria must not be initiated on treatment and must be withdrawn from the study as a screen failure. If a subject, who in error is assigned a randomization number or incorrectly started on treatment, in spite of not

meeting all of the inclusion/exclusion criteria, will be withdrawn from the study and the assigned randomization number will not be re-assigned to another subject and the subject will not be counted toward any treatment cohort.

6.2 Dosage and Administration

This is a phase Ib, open label dose escalation and safety evaluation of durvalumab (MEDI4736) and oral decitabine (ASTX727) combination therapy. This trial opened with the administration of subcutaneous (SC) injection of azacitidine. Treatment i.e. 5 to 10 daily visits for a large-volume SC injection continuing for several months or even years, represents a significant hardship for patients. A possible consequence is non-compliance or earlier discontinuation of a beneficial treatment. Successful development of an oral DNA methyltransferase inhibitor eases the burden of long duration SC therapy, particularly for those patients who are benefiting the most and need continuing treatment for long periods. In our trial with SC injection of azacitidine, we were achieving global tumor hypomethylation with clinical benefit. Furthermore, a tolerable AE profile was being observed. These preliminary results rationalize the continuation of this study but with an oral DNA methyltransferase inihibitor for reasons stated above. Since the oral DNA methyltransferase inhibitor is an investigational drug, we will administer the oral drug with the FDA approved durvalumab. We will continue treatment of azacitidine SC for those patients already enrolled into the study. However, all newly enrolled patients will receive an oral tablet of ASTX727 (35 mg decitabine/100 mg cedazuridine) daily on either Days 1-3, Days 1-4, or Days 1-5, and durvalumab (MEDI4736) 1500 mg via IV infusion x 1 in a 4 week cycle. Oral decatibine (ASTX727) will be administered alone in Cycle 1 and the combination of oral decatibine (ASTX727) and durvalumab therapy will be given in Cycles 2-12 or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met, whichever occurs first. The BED will be assessed on pre-treatment and post-treatment biopsies obtained at week 8. BED is defined as the dose of oral decatibine (ASTX727) that results in at least a 10% decrease in LINE-1 methylation from the baseline biopsy sample to the 8-week on-treatment tumor biopsy sample in at least 50% of patients treated within the same dose level. Accrual will be suspended until assessment of the LINE-1 methylation levels in the first 2 dose cohorts. If the BED has not been determined in the first 2 dose levels and it is safe to do so, then the study will re-open to accrual and a subsequent group of 3 patients will receive the 3rd dose level. If both the first 2 dose levels result in $\geq$ 10% decrease in LINE-1 methylation, then the dose which induces the greatest fold change in HLA Class I/II APM expression and/or CD8+ T cell infiltration and with the lowest AE profile will be the dose utilized for the dose expansion group. Dose Limiting Toxicity (DLT) will be assessed through 28 days post Cycle 2.

Although assessment of the BED is primary, the dose also needs to be safe. Each dose will be assessed for safety according to a stopping rule and a DLT toxicity definition as outlined in the protocol and statistical section. Decisions will then be made about dose escalations of oral decatibine (ASTX727). Subjects will be sequentially assigned to the cohorts. The first 6 enrolled subjects will ingest one tablet daily on Days 1-3 of a 28-day cycle. If two or more of the first six subjects experience a DLT, then the dose will be reduced and an additional six patients will be treated at the reduced dose. If two or more of the six at the reduced dose experience a DLT, then the study will be terminated. If at any time during accrual to a cohort, 2 or more patients in a cohort experience DLT, enrollment to that cohort will be terminated. If less than two of the six patients treated at dose level 1 experience a DLT, a subsequent group of six patients will receive dose level 2.

Patients cannot change groups or dose assignments upon the initiation of the study protocol. Please refer to **Sections 5.1.2, 5.1.3, and 5.2.4**. for the administration and monitoring of administration of durvalumab (MEDI4736) and tremelimumab. Please refer to **Section 5.3** for the administration and monitoring of administration of oral decitabine (ASTX727).

Table 5a: Cohort size and dose escalation for oral decitabine (ASTX727)

Cohort (# of pts)	Oral decitabine (ASTX727) (28 day cycle)	Grade 3 or higher	2-fold DNMT1 inhibition in ≥50% of patients
BD-1 (6)	ASTX 727 one tablet daily on Days 1-2	MTD[1]	BED[2]
B1 (6)	ASTX 727 one tablet daily on Days 1-3	MTD[1]	BED[2]
B2 (6)	ASTX 727 one tablet daily on Days 1-4	MTD[1]	BED[2]
B3 (6)	ASTX 727 one tablet daily on Days 1-5	MTD[1]	BED[2]

[1]MTD (maximally tolerated dose) will be defined as that dose of azacitidine that results in ≤2 of 6 patients experiencing a DLT
[2]BED (biologically effective dose) will be defined as that dose of oral decitabine (ASTX727) that results in at least a 10% decrease in LINE-1 methylation in pre- and on-treatment biopsy samples in >50% of treated subjects

Table 5b: Cohort size and dose escalation for azacitidine

Cohort (# of pts)	Azacitidine (28-day cycle)	Grade 3 or higher	2-fold DNMT1 inhibition in ≥50% of patients
D-1 (6)	20 mg/m2 on Days 1-5	MTD[2]	BED[3]
1 (6)	40 mg/m2 on Days 1-5	MTD[2]	BED[3]
2 (6)	40 mg/m2 on Days 1-5 and 8-12	MTD[2]	BED[3]
3 (6)	75 mg/m2 on Days 1-5	MTD[2]	BED[3]

The overall safety of the combination therapy will be evaluated by following patients up to 28 days for DLTs after the first dose of oral decitabine (ASTX727) and durvalumab (MEDI4736) combination therapy (end of cycle 2 (which is the first cycle of the combination)).

6.3 Dose Escalation Decision Rules

Dose escalation monitoring

In order to ensure that patients are receiving the assigned dose of drug, oral decitabine (ASTX727), several measures will be employed.

Printed orders will be available.

The principal investigator, research nurse, and data manager will review the available toxicity data prior to continuing to escalate the dose and enrolling patients into the new cohort.

Prior to the start of each new dose level (i.e. accrual of a new cohort), a dated letter will be sent to the pharmacy which describes the change in dose.

Stopping rules

Dose escalations will continue until one of the following stopping rules has been satisfied:

1.The BED has been determined.
2.If at any time during accrual to a cohort, 2 or more patients in a dose cohort experience DLT, enrollment to that dose cohort will be terminated and dose escalation will stop.
3. Two of six patients treated at a reduced dose of oral decitabine (ASTX727) on Days 1-2 of a 28 day cycle experience a DLT

6.3.1 Definition of BED

Biologically effective dose (BED) is defined as the dose of oral decitabine (ASTX727) that results in at least a 10% decrease in LINE-1 methylation level from the baseline sample to the 8 week post baseline tumor sample in at least 50% of patients treated within a dose level. As LINE-1 (long interspersed element-1) is a repetitive DNA retrotransposon that duplicates via a copy-and-paste genetic mechanism. As LINE-1 constitutes approximately 17% of the human genome, the extent of LINE-1 methylation is regarded as a surrogate marker of global DNA methylation. ASTX Pharmaceuticals has assessed changes in LINE-1 methylation with ASTX727 as a marker of efficacy in their prior clinical trials. The change in LINE-1 methylation is a working rule and a panel of markers will be assessed and the dose with the most viable panel and lowest adverse event profile will be used in the expansion cohort of the study.

6.4 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the dose escalation phase of the trial. The period for evaluating DLTs will be from the time of first administration of oral decitabine (ASTX727) until after 28 days after the first dose of oral decitabine (ASTX727), durvalumab (MEDI4736), and tremelimumab combination therapy (end of Cycle 2 (which is the first cycle of the triple combination)).

Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. 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. 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 $\geqslant$ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to $\leqslant$ 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 $\leqslant$ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any $\geqslant$ Grade 3 non-irAE, except for the exclusions listed below
- Grade 4 neutropenia lasting > 10 days or accompanied by fever (defined as > 38.5°C requiring

hospitalization)

- Grade 3 thrombocytopenia with clinically significant bleeding

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 (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- 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
- Grade 3 emesis that responds to optimal antiemetic therapy within 72 hours
- Grade 3 diarrhea that responds to optimal medical management within 72 hours

Immune-related AEs are defined as AEs of an immune nature (ie, 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.

If a DLT occurs, the patient will be removed from further treatment in the protocol. The patient will be followed for their DLT until there is complete resolution of the observed toxicity. These toxicities will effect dose escalation decisions. Any occurrence of grade 4 or greater toxicity will prompt the sponsor and the principal investigator to conduct a thorough evaluation of the available safety information to justify a decision to enroll new subjects into the study.

6.5 Dose Modification and Toxicity Management

6.5.1 Durvalumab (MEDI4736) and tremelimumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab (MEDI4736) 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 (MEDI4736) or tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (MEDI4736) and tremelimumab (see Appendix 1).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab (MEDI4736) or tremelimumab should be permanently discontinued.

Following the first dose of durvalumab (MEDI4736) or tremelimumab, subsequent administration of durvalumab (MEDI4736) or tremelimumab can be modified based on toxicities observed (see Appendix 1). Reductions in the dose administered are not permitted.

Based on the mechanism of action of durvalumab (MEDI4736) or tremelimumab 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 Appendix 1.

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.

6.5.2 Azacitidine/Oral decitabine (ASTX727)

6.5.2.1 Dose Adjustment Guidelines

A maximum of 1 dose reduction will be allowed from the original dose. Please refer to **Table 2** for the dose cohorts.

Azacitidine or oral decitabine may be withheld for up to 7 days between the end of 1 cycle and the start of the next cycle to allow hematologic criteria to recover sufficiently for the next cycle to begin.

The maximum number of days that a azacitidine or decitabine dose may be withheld without requiring a dose reduction is 7 days.

The maximum number of days that azacitidine or oral decitabine may be withheld due to unacceptable toxicity before a subject is permanently discontinued from the study is 14 days.

For the purposes of dose adjustments, unacceptable toxicity will be defined as any AE that is deemed by the Investigator to be related to azacitidine or oral decitabine (ASTX727) that poses a medical risk or substantial discomfort to the subject including, but not limited to, Grade 3 or 4 hematologic or non- hematologic toxicity. Subjects should be discontinued after the 3rdepisode.

Please refer to Table 6 for the Dose Adjustment Guidelines due to unacceptable toxicity.

Table 6: Dose Adjustments and Dose Delays for Toxicity

Toxicity	**Recommendation**
Grade 2 hematologic toxicity causing delay to the planned start of a Cycle Absolute Neutrophil Count (ANC) < 1.0 x 10^9/L Platelets < 75 x 10^9/L	Hold azacitidine or decitabine until ANC & Platelets ≥ 1.0x10^9/L Delay ≦ 7 days, resume azacitidine or decitabine at same dose Delay 8 – 14 days, reduce azacitidine ordecitabine by a dose cohort level Delay ≥ 14 days, permanently discontinue azacitidine or decitabine
Grade 3 neutropenia or thrombocytopenia causing delay to the planned start of a Cycle ANC 0.5-0.99 x 10^9/L Platelets 25-49 x 10^9/L	Hold azacitidine or decitabine until ANC & Platelets recover to ANC ≥ 1.0 x 10^9/L, Platelets ≥ 75 x 10^9/L) Recovery in ≤ 7 days, resume azacitidine or decitabine at same dose Recovery in 8–14 days, reduce azacitidine or

	decitabine by a dose cohort level No recovery by 14 days, permanently discontinue azacitidine or decitabine_
Grade 4 neutropenia or thrombocytopenia causing delay to the planned start of a Cycle ANC < 0.5 x 10^9/L Platelets < 25 x 10^9/L For ANC < 0.5 x 10^9/L The initiation of G-CSF is left at the Investigator's discretion. If initiated administer G-CSF per institutional practice or package insert and continue until ANC recovers to ≥ 2.0 x 10^9/L	Hold azacitidine or decitabine until ANC & Platelets recover to ≤ Grade 1 (ANC ≥ 1.5 x 10^9/L, Platelets ≥ 75 x 10^9/L) Recovery in ≤ 7 days, reduce azacitidine or decitabine by a dose cohort level No recovery by 7 days, permanently discontinue azacitidine or decitabine
Grade 3 or 4 Nausea or Vomiting Grade 3 or 4 Diarrhea Grade 3 or 4 Fatigue/Asthenia	Hold until resolution to ≤ Grade 1 and provide optimal medical management. If response ≤ 72 hours (3 days), and recovery ≤ 7 days, reduce azacitidine or decitabine by a dose cohort level If event recurs after re-challenge at reduced dose, discontinue azacitidine or decitabine. If no recovery by 7 days, discontinue azacitidine or decitabine.
Grade 3 or 4 any other non-hematologic toxicity	Hold until resolution to ≤ Grade 1 and provide optimal medical management. If recovery ≤ 7 days, reduce azacitidine or decitabine by a dose cohort level. If event recurs after re-challenge at reduced dose, discontinue azacitidine or decitabine If no recovery by 7 days,

	discontinue azacitidine or decitabine

ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; G-CSF = granulocyte colony stimulating factor.
Note: The initiation of G-CSF is left at the Investigator's discretion.
Note: Granulocyte colony stimulating factor (G-CSF) should only be utilized in accordance to ASCO or ESMO recommendations.
Note: If Grade 3 or 4 neutropenia associated with fever or Grade ≥ 3 thrombocytopenia with clinically significant bleeding occurs at any time, the dose adjustment guidelines for Grade 4 hematological toxicity should be enacted.
Note: If neutropenia is associated with fever and severe diarrhea, subject should be managed appropriately according to the local practice. In case of recurrence of the diarrhea with neutropenia and fever, the continuation of the subject in the study should be discussed on a case-by-case basis with the sponsor's study monitor.
Note: Any Grade 3 or 4 toxicity that is not clinically significant, as judged by the treating physician and/or PI, does not require any dose reductions of azacitidine or decitabine.

6.5.2.2 Dose Adjustment Based on Hematology Toxicity

Hematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets fall below 50.0 x 10^9/L and/or ANC below 1.0 x 10^9/L. Recovery is defined as an increase of cell line(s) where hematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (ie, blood count at recovery ≥ nadir count + [0.5 x (baseline count – nadir count)]. Please refer to the Table in Section 2.3 of the PI.

For Patients Without Reduced Baseline Counts: WBCs ≥ 3.0 x 10^9/L, ANC ≥ 1.5 x 10^9/L, and Platelets ≥ 75.0 x 10^9/L:

If hematological toxicity is observed following azacitidine or decitabine treatment, the next cycle of azacitidine or decitabine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced.

Following dose modifications, the cycle duration should return to 28 days.

For Patients with Reduced Baseline Blood Counts: WBC < 3.0 x 10^9/L, ANC < 1.5 x 10^9/L, and Platelets < 75.0 x 10^9/L:

Following azacitidine or decitabine treatment, if the decrease in WBC or ANC or platelets from baseline is less than 50%, or greater than 50% but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine or decitabine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced). Following dose modifications, the cycle duration should return to 28 days.

6.5.2.3 Missing Doses

All efforts should be made to administer IP on all of the scheduled days of each 28-day treatment cycle. Patients who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume treatment with their assigned IP and complete the 12-month treatment period. Any missed doses during that period should not be added after the last scheduled day of administration to compensate for missed doses.

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

7.1 Restrictions during the study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 4) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of study drug; 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. Male partners of a female subject must use male condom plus spermicide throughout this period.

- Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete

hysterectomy) or post-menopausal (defined 12 months with no menses without an alternative medical cause).

Non-sterilized males who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 180 days after receipt of the final dose of study drug. Female partners of a male subject must use a highly effective method of contraception throughout this period.

Highly effective methods of contraception are described in Table 4. A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Restrictions relating to concomitant medications are described in Section 7.2.

Table 7 Highly Effective[a] Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[b]	• Etonogestrel implants: e.g. Implanon or Norplan • Intravaginal device: e.g. ethinylestradiol and etonogestrel • Medroxyprogesterone injection: e.g. Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

Table 7 Highly Effective[a] Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods

[a] Highly effective (i.e. failure rate of <1% per year)

[b] 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 (MEDI4736) or tremelimumab or 28 days following the last dose of azacitidine or decitabine, whichever is the longest time period.

7.2 Concomitant treatment(s)

The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.6 for guidance on management of IP-related toxicities.

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.

Antiemetics are not required during the study; however, at the Investigator’s discretion, subjects may receive prophylactic antiemetics approximately 30 minutes prior to each dose of azacitidine or decitabine.

Treatment with antidiarrheal medications should be prescribed at the first sign of diarrhea. Pre-medication with antidiarrheal medication for subsequent doses of azacitidine or decitabine may be appropriate at the Investigator’s discretion.

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, other than any stated combination regimens. Concurrent use of hormones for non cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated non-target lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy)

3. Any decitabine, or other demethylating or histone deacetylating agents.

4. 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).

5. Live attenuated vaccines within 30 days of durvalumab (MEDI4736) and tremelimumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab (MEDI4736) and tremelimumab for 30 days post discontinuation of durvalumab (MEDI4736) and tremelimumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

6. Drugs known to be metabolized by CDA (eg, cytarabine, gemcitabine, azacitidine, vidarabine, zalcitabine, zidovudine, telbivudine, didanosine, stavudine, lamivudine, abacavir, emtricitabine, entecavir, apricitabine, idoxuridine, trifluridine, tenofovir, and adefovir) should not be administered on the same days with cedazuridine or ASTX727.

Table 8. Prohibited and Rescue Medications

Prohibited medication/class of drug:	Usage:
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment through 90 days after the last dose of IP.
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (including SoC). (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor α blockers	Should not be given whilst the patient is on IP treatment (including SoC). (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC) during the study

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

Rescue/supportive medication/class of drug:	Usage:
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc])	Should be used when necessary for all patients

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 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 prior to study registration, 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 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. An archived pre-treatment tumor biopsy obtained outside of the 28-day screening window may be used for PD-L1 staining if the subject has not received any interval treatment since undergoing the biopsy.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Adverse event/serious adverse event assessment with prior immunotherapy
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height

- 12-lead ECG (in triplicate [2-5 minutes apart])
- Tumor biopsy
- Peripheral blood draw for research analysis
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Bone scan
- 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 B and C serologies
    - HIV testing
    - Urinalysis (see Table 9)

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) of protocol treatment do not need to be repeated on C1D1. The treatment to be used in this trial is outlined below in **Table 6**.

- Complete physical exam
- Vitals signs and weight
- 12-lead ECG (in triplicate [2-5 minutes apart]), as clinically indicated
- ECOG Performance Status
- Adverse event/serious adverse event assessment
- Review of prior/concomitant medications
- Clinical laboratory tests for:
    - Hematology (see Table 7)
    - Clinical chemistry (see Table 8)
    - TSH
    - Coagulation (PT, PTT, INR), as clinically indicated
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Urinalysis (see Table 9)

- Pharmacokinetic assessment
- Imaging by CT/MRI
- Bone scan, if baseline bone scan demonstrates metastatic disease
- Tumor biopsy sample for research analysis
- Peripheral blood draw for research analysis

Table 9 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Durvalumab (MEDI4736)	1500 mg	Q4W	IV infusion	Day 1 of each 4 week cycle for 12 cycles [a]	Experimental
Tremelimumab	75 mg	Q4W	IV infusion	Day 1 of each 4 week cycle for 4 cycles [a]	Experimental
Tremelimumab	300 mg	Once	IV infusion	Day 1 of Cycle 2	Experimental
Azacitidine	40 mg/m2 or 75 mg/m2	QD	SC	Days 1-5 or Days 1-5 and 8-12 of each 4 week cycle for 12 cycles [a]	Experimental
Decitabine (ASTX727)	35 mg decitabine	QD	PO	Days 1-3, 1-4, or 1-5 of each 4-week cycle for 12 cycles[a]	Experimental

[a]Azacitidine or decitabine will be administered alone in Cycle 1. For those patients receiving azacitidine, the combination of azacitidine, durvalumab, and tremelimumab therapy will start in Cycle 2. Patients will continue with azacitidine, durvalumab and tremelimumab combination therapy for Cycles 3-5 and azacitidine and durvalumab for Cycles 6-12. For those patients receiving decatibine, the combination of decatibine and durvalumab therapy will be given in Cycles 2-12.

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 azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), or tremelimumab prior to completing the 12 months of treatment with combination therapy, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures must be completed within ± 28 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 azaciditine, or oral decitabine, durvalumab (MEDI4736), and tremelimumab treatment and achieved disease control, or have discontinued

azaciditine, or decitabine, durvalumab (MEDI4736) or tremelimumab due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX 2

Assessments for subjects who have discontinued azaciditine, or decitabine, durvalumab (MEDI4736), or tremelimumab treatment due to confirmed PD are presented in **Appendix 3**.

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 Assessments.

8.2.2 Physical examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10

8.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.0.

8.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

On infusion days, patients receiving durvalumab (MEDI4736) + tremelimumab treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving durvalumab (MEDI4736) + tremelimumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]).

Approximately 30 minutes +/- 5 minutes during the infusion (**halfway** through infusion).

At the end of the infusion (approximately 60 minutes +/-5 minutes).

In the 1-hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of infusion) (+/- 5 minutes) is required after the first infusion of durvalumab (MEDI4736) and tremelimumab and then for subsequent infusions as clinically indicated.

If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes +/- 5 minutes after each durvalumab (MEDI4736) and tremelimumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Body weight is also recorded along with vital signs on the days of infusion of durvalumab +/- tremelimumab.

Situations in which vital signs results should be reported as AEs are described in Section 10.3. 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.

8.2.5 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- 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

Table 10. 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 11. 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 screening, Cycle 1 Day1, and as clinically indicated

Table 12. 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

8.3 Biological sampling procedures

8.3.1 Biomarker sampling and evaluation methods

A tumor biopsy will be obtained pre- and either on- or post-treatment while on the study. A biopsy will be obtained on week 8 during the phase 1b dose-escalation portion of the study. The tumor samples will be evaluated for changes in LINE-1 methylation and/or expression of CD8+ T cells and MHC Class I/II by immunofluorscent staining and quantitative analysis. Other immune biomarkers which will be evaluated include, but are not limited to: PD-1, PD-L1, PD-L2, CD80, CD4, CD8, FoxP3, CTLA-4, Lag-3, Tim-3, IFN-g, and HPV-specific CD8+ T cells for HPV-associated tumors.

In addition, blood and stool samples for correlative biomarker studies will be collected at pre- and either on- or post-treatment. The blood will be evaluated for changes in circulating HPV-specific CD8+ T cells, for tumor DNA circulating markers, and cytokines. The stool will be used to characterize the microbiome in the gut and the microbiome correlated with response to immunotherapy.

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab (MEDI4736) and/or tremelimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm.

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 a less than 3 months old is not available, patients can be asked to 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 the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. 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.

8.3.2 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 13. Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	**Clinical chemistry**	5	12	60
	Hematology	5	12	60
Biomarker		50	2	100
Total				220

8.3.3 Archival tumor samples and fresh tumor biopsies

8.3.3.1 Archival tumor samples

A pre-treatment tumor biopsy sample will be retrieved when available, either as a formalin-fixed paraffin-embedded (FFPE) tissue block or up to 20 unstained slides. The archival tumor biopsy sample will be shipped to and stored in the laboratory of Dr. Pai for analysis. Analyses which will be conducted include, but are not limited to, LINE-1 methylation status, PD-L1 expression, tumor mutation analysis, RNA analysis, and MHC Class I/II and CD8+ T cell immunohistochemistry. After the clinical study report has been finalized, the archival FFPE will be returned to the original hospital, if requested, and any unstained slides will be retained for future research.

8.3.3.2 Fresh tumor biopsies

A fresh tumor biopsy will be obtained in all subjects pre-treatment and either on- or post-treatment, if safely accessible for biopsy as determined by the treating physician. A biopsy will be obtained on week 8 during the phase 1b dose-escalation portion of the study. The fresh tumor biopsy sample will be shipped to and stored in the laboratory of Dr. Pai for analysis. Analyses which will be conducted include, but are not limited to, LINE-1 methylation, PD-L1 expression, tumor mutation analysis, RNA analysis, and MHC Class I, II and CD8+ T cell immunofluorescence. The pre-, on- or post-treatment biopsy can only be waived if the location

of the lesion is not safely accessible for biopsy, as determined by the treating physician. The on-treatment biopsy will be performed at the time of confirmed PR on imaging, as outlined above. For the non-superficial lesions, the on-treatment core needle biopsy will be performed under image guidance, either CT, MRI, or ultrasound. For dermal lesions, a core needle, excisional, or punch biopsy can be performed without image guidance. Biopsies will be obtained of lesion(s) which have decreased in size. A biopsy of a progressing lesion can also be obtained at the same time based on the discretion of the physician performing the procedure and the Investigator. Any biopsied lesion(s) can no longer be included in the objective tumor response assessment except for those patients whom only have one target lesion which is greater than 2 cm in diameter in any one direction. A post-treatment biopsy will be obtained in those patients who stop study treatment prior to completing 12 months of therapy or any patients who completes 12 months of therapy but did not undergo an on-treatment biopsy. Patients who had an on-treatment biopsy may undergo a post-treatment biopsy at the time of completing 12 months of therapy; however, this is not a mandatory biopsy. Any patient who restarts treatment will require another biopsy prior to restarting treatment. The fresh tumor biopsy sample will be shipped to and stored in the laboratory of Dr. Pai for analysis. At a minimum, 3 core biopsies will be obtained and 1 core will be formalin fixed and the other 1-2 cores will be flash frozen. Analyses which will be conducted include, but are not limited to, LINE-1 methylation, PD-L1 expression, tumor mutation analysis, RNA analysis, and MHC Class I/II and CD8+ T cell immunohistochemistry. After the clinical study report has been finalized, any retaining tissue will be retained for future research.

8.3.4 Stool Collection

The subject(s) will be given kits for the collection of stool pre-treatment and at Week 8 (+/- 7 days). The stool samples will be shipped to the Broad Institute for sequencing of the microbiota flora in the stool.

8.3.5 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.

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

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino 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 study may wish to implement the following 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 (MEDI4736), tremelimumab, and azacitidine or oral decitabine (ASTX727) would continue between the initial assessment of progression and confirmation for progression.

- In addition, subjects may continue to receive durvalumab (MEDI4736), tremelimumab, and azacitidine or oral decitabine (ASTX727) 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 (MEDI4736), tremelimumab, and azacitidine or oral decitabine (ASTX727) 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 (MEDI4736) + tremelimumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.1.1 Response Assessments

Response assessments (tumor evaluations) should be performed at screening within 28 days before the start of IP, and every 8 weeks (± 7 days) from Cycle 1 Day 1 until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Subjects with historical tumor scans evaluable per RECIST v1.1 performed ≤ 28 days before the first dose need not repeat scans for the purposes of screening. Evaluation of response should be performed using the modified RECIST guidelines, as described above and by Investigator assessment.

Response will be assessed using RECIST v1.1, according to Investigator assessment. Response assessments include computed tomography (CT) scan or magnetic resonance imaging (MRI) of the neck with supraclavicular node imaging, the chest and abdomen/pelvis, neurological examination with facial nerve evaluation, and bone scans at baseline for all subjects. Bone scans will be repeated only if the subject is symptomatic or with known bone metastasis, per standard of care.

The same mode of imaging for lesion evaluation at screening must be used consistently throughout the study. Adherence to the planned imaging schedule is critical regardless of dose delays or unscheduled or missed assessments.

The CT imaging should include contrast unless medically contraindicated. Conventional CT should be performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

All subjects with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as SD for a best response.

Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from durvalumab (MEDI4736), tremelimumab, and azacitidine or oral decitabine (ASTX727) treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix 3).

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 (ie, 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.

10.1.3 Durvalumab (MEDI4736) + tremelimumab adverse events of special interest

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 (MEDI4736) and tremelimumab 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 (MEDI4736) 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 (MEDI4736) and tremelimumab include:

- Diarrhea / Colitis and intestinal perforation

- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye,skin, haematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab (MEDI4736) and tremelimumab Investigator Brochures. More specific guidelines for their evaluation and treatment are described in detail in Table 1.

10.1.4 Immune-related adverse events

Based on the mechanism of action of durvalumab (MEDI4736) and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al 2010, Braakhuis et al, 1998

Braakhuis, B. J., van Dongen, G. A., van Walsum, M., Leyva, A., and Snow, G. B. Preclinical antitumor activity of 5-aza-2'-deoxycytidine against human and neck cancer xenografts [corrected]. Invest New Drugs, 6: 299-304, 1988.

Brahmer et al 2012, Topalian et al 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab (MEDI4736) or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Table 3, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Weber et al 2012). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab or mycophenolate).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician.

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 9.2.1. 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. Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.2 Assessment of relationship

The Investigator must determine the relationship between the administration of investigational product and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: Means a causal relationship of the adverse event to investigational product administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a reasonable possibility that the administration of investigational product caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the investigational product and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to an investigational product, the name of the manufacturer (Astrazeneca/MedImmune or ASTX Pharmaceuticals) will be included when reporting the event.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded in electronic CRFs 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 and ASTX Pharmaceuticals 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 grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab (MEDI4736) or tremelimumab (yes or no) or oral decitabine (ASTX727) (yes or no)
- Action taken with regard to durvalumab (MEDI4736) + tremelimumab combination or azacitidine or oral decitabine (ASTX727) agent
- 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
- AE is serious due to <<criteria>>
- 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 durvalumab (MEDI4736), tremelimumab, or azacitidine or oral decitabine (ASTX727)

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 (MEDI4736) + tremelimumab and 28 days after the last dose of azacitidine or oral decitabine (ASTX727)).

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.

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 eCRF. 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.

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 azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736) + tremelimumab. 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 should 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 study drug is administered through 90 days after the last dose of durvalumab (MEDI4736) + tremelimumab, 28 days after the last dose of azacitidine or oral decitabine (ASTX727), 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/AdEERs 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 and ASTX Pharmaceuticals. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca and ASTX Pharmaceuticals 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 and ASTX Pharmaceuticals at the same time.

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

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-15-11430)

***** 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.

10.3.2.1 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab (MEDI4736) + tremelimumab 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 (MEDI4736) and tremelimumab or 28 days post-last-dose of azacitidine or oral decitabine

(ASTX727) safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

10.3.3 Other events requiring reporting

10.3.3.1 Overdose

An overdose is defined as a subject receiving a dose of durvalumab (MEDI4736), tremelimumab, or azacitidine or oral decitabine (ASTX727) in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of durvalumab (MEDI4736), tremelimumab, or azacitidine or oral decitabine (ASTX727) assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Any overdose of a study subject with durvalumab (MEDI4736), tremelimumab, or azacitidine or oral decitabine (ASTX727), with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor, 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 10.3 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab (MEDI4736), tremelimumab, or azacitidine or oral decitabine (ASTX727).

The investigator will use clinical judgment to treat any overdose.

10.3.3.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.) 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.

10.3.3.3 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

10.3.3.3.1 Maternal exposure

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of reproductive potential, regardless of disease state) occurring while the subject is on IP, or within 90 days of the subject's last dose of IP, are considered immediately reportable events. The IPs should be discontinued immediately.

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, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist, or another appropriate healthcare professional for further evaluation.

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. The Investigator will follow the female subject until completion of the pregnancy outcome and up to 1 year to monitor the baby,

and must notify AstraZeneca Patient Safety within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form and Infant Follow-Up Form, or approved equivalent form.

Congenital abnormalities or birth defects, stillbirth, neonatal death, spontaneous or therapeutic abortion or miscarriage should be reported and handled as SAEs using the SAE Report Form, or approved equivalent form. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Astrazeneca Patient Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form. 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.

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.

10.3.3.3.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of study drug.

Pregnancy of the patient's partner is not considered to be an AE. However, if a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately. In addition, 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

Rational for Changes from SC Injection to Oral Drug
This trial opened with use of subcutaneous (SC) injection of azacitidine. Treatment, ie, 5 to 10 daily visits for a large-volume subcutaneous injection continuing for several months or even years, represents a significant hardship for patients. A possible consequence is non-compliance or earlier discontinuation of a beneficial treatment. Successful development of an oral DNA methyltransferase inhibitor will ease the burden of long-duration SC therapy, particularly for those patients who are benefitting the most and need continuing treatment for long periods.

The primary objective and design and number of doses to be tested with oral decitabine remain the same as in the original protocol which used SC injection of azacitidine. The overall sample size has been revised to account for accrual of patients who receive oral decitabine in addition to the patients accrued when the original protocol opened using SC injection of azacitidine.

The primary objective of the phase I trial is to determine the BED. The BED is to be determined among evaluable patients (eligible patients who at least begin protocol treatment and have an evaluable pre- and on-treatment (8-week) biopsy sample available). Three doses of oral decitabine (ASTX727) are scheduled to be tested. BED is defined as the dose of oral decitabine (ASTX727) that results in at least a 10% decrease in LINE-1 methylation from the baseline biopsy to the 8-week on-treatment tumor biopsy in at least 50% of patients treated within the same dose level. If the BED has not been determined in the first 2 dose levels and it is safe to do so, then the study will re-open to accrual and a subsequent group of 3 patients will receive the 3rd dose level. IF both the first 2 dose levels result in $\geq$ 10% decrease in LINE-1 methylation, then the dose which induces the greatest fold change in HLA Class I/II APM expression and/or CD8+ T cell infiltration and with the lower adverse event profile will be the dose utilized for the dose expansion cohort. The change is a working rule and a panel of markers will be assessed and the dose with the most viable panel and lowest adverse event profile will be used in the expansion cohort.

Although assessment of the BED is primary, the dose also needs to be safe. Each dose will also be assessed for safety. Six patients will be entered into dose level 1. Adverse events (i.e. dose limiting toxicity (DLT) assessment as defined in section 6.4) will be assessed through 28 days post cycle 2. If two or more of the first six subjects experience a DLT, then the dose will be reduced and an additional six patients will be treated at the reduced dose. If two or more of the six at the reduced dose experience a DLT, then the study will be terminated. If at any time during accrual to a dose cohort, 2 or more patients in a dose cohort experience DLT, enrollment to that dose cohort will be terminated. If less than two of the six patients treated at dose level 1 experience a DLT, a subsequent group of six patients will receive dose level 2.

Accrual will be suspended until review of the BED rate in tissue from baseline and 8 weeks post baseline has been completed from patients entered into the first 2 dose levels. If the BED has not been determined in the first 2 dose levels and it is safe to do so, then the study will re-open to accrual and a subsequent group of 6 patients will receive the 3rd dose level. Once the BED is determined, dose escalation will stop and the BED will be used in the expansion cohort.

Approximately 28 evaluable patients (eligible patients who at least begin protocol treatment and have an evaluable pre- and on-treatment (8-week) biopsy sample available) are estimated to be accrued during the BED assessment phase with the oral decitabine. This is based on studying 6 evaluable patients per dose level with a total of 3 dose levelsand an additional 10 evaluable patients entered at the BED ('expansion cohort' accrued to ensure that the BED rate is acceptable). The further assessment of the BED will be based on studying these 10 additional patients. Additional subjects may be enrolled into the cohort(s) to ensure that the required number of evaluable pre- and on-treatment biopsy samples are available to adequately determine the BED. See end of this statistical section for overall sample size.

BED is defined as outlined above. Six evaluable patients are estimated to be accrued per dose level with the additional 10 evaluable patients in the expansion cohort. The below table gives the probabilities of observing at least 33% of patients within a dose level with the BED for the first 6 patients for varying true rates of the BED.

True BED rate	Probability of ≥2 out of 6 patients in a dose level meet BED definition.	Probability of ≥7 out of 16 meet BED definition (given that ≥2 out of 6 patients in the dose level from original testing meet the BED definition plus the expansion cohort)
50%	.89	.73
55%	.93	.84
60%	.96	.92

For example, if the true rate of BED is 50%, the probability of observing ≥2 out of 6 patients in a dose level with the BED is 89%. The above table also shows the probabilities of successfully declaring the BED after cohort expansion (the additional 10 patients to a dose level) (last column). With 6 patients entered in a dose level and 10 in the expansion cohort (with cutpoints as in the above table), if the true BED rate were instead as low as 27%, the probability of a dose level being used as the BED in the phase II portion of this trial is only 10%.

With an estimated monthly accrual of 2 patients, accrual with use of the oral agent is estimated to complete in approximately 9 months. As of October 1, 2019, n=11 patients have been registered

to receive SC injection of azacitidine. Accrual for patients to receive SC injection of azacitidine continues during review and approval of this amendment to change to administration of oral decitabine. With approximately 2-3 more patients enrolled to receive SC injection of azacitidine during amendment review, a total of up to N=41 (13 SC injection of azacitidine + up to 28 oral decitabine) patients could be entered.

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

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.3 Informed consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.4 Changes to the protocol and informed consent form

Any changes made to the protocol and informed consent form must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

12.5 Audits and inspections

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13 STUDY MANAGEMENT

a. Data Reporting

i. Method

The QACT will collect, manage, and monitor data for this study.

13.1.2 Data Submission

The schedule for completion and submission of case report forms (electronic) to the ODQ (Office of Data Quality) is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with ODQ
On Study Form	Within 14 days of registration

Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

b. Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet approximately quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

c. Monitoring of the study

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

14. DATA MANAGEMENT

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the electronic-based case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x rays.

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

For the purposes of data analysis associated with the publication of the final manuscript and requirements from the journal review of the manuscript, the Investigator/Study PI will be able to extract data from the EPIC medical records of participants to supplement the information available in Inform. The extracted information will include details about HPV status, therapies received after the completion of treatment or following progression; details regarding prior chemotherapy and radiation treatments for R/M disease; primary therapies and duration of therapies for the patient’s disease prior to development of R/M. In addition, the Investigator/Study PI will access Hematology labs within EPIC to determine what peripheral blood analysis was performed.

a. Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives, respectively, 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

a. Identity of investigational product(s)

Table 44. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab (MEDI4736)	1500 mg, solution, IV	MedImmune
Tremelimumab	75 mg, solution, IV	MedImmune
Tremelimumab	300 mg, solution, IV	MedImmune
Azacitidine	40 mg/m2 or 75-mg/m2, suspension, SC	Celgene
Decitabine	35 mg decitabine/100 mg cedrizine, PO	ASTX Pharmaceuticals

16. LIST OF REFERENCES

ASHSP 2006
American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs 2006.

Andorsky et al 2011
Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, and Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res. 2011. 17(13):4232-4244

Antonia et al 2014b
Antonia S, Ou SI, Khleif SN, Brahmer J, Blake-Haskins A, Robbins PB, et al. Clinical activity and safety of MEDI4736, an anti-programmed cell death ligand-1 (PD-L1) antibody in patients with NSCLC. Poster presented at the European Society for Medical Oncology (ESMO) Meeting; 2014 Sep 26-30; Madrid, Spain.

Antonia et al 2014a
Antonia S, Goldberg S, Balmanoukian A, Narwal R, Robbins P, D'Angelo G, et al. A Phase 1 open-label study to evaluate the safety and tolerability of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in combination with tremelimumab in patients with advanced non-small cell lung cancer (NSCLC). Poster presented at European Society of Medical Oncology (ESMO) Meeting; 2014 Sep 26-30; Madrid, Spain.

Antonia et al 2015
Antonia et al. Phase ib study of medi4736 in combination with treme in patients with advanced NSCLC. Chicago, Il ASCO May30-June4,ASCO 2015, poster #3014.

Aparicio et al, 2002
Aparicio, A. and Weber, J. S. Review of the clinical experience with 5-azacytidine and 5-aza-2'-deoxycytidine in solid tumors. Curr Opin Investig Drugs, 3: 627-633, 2002.

Bast et al, 2008
Bast, R. C., Iyer, R. B., Hu, W., Kavanagh, J., Coleman, R. L., Levenback, C., Sood, A. K., Wolf, J., Gershenson, D. M., Markman, M., and Fu, S. A phase IIa study of a sequential regimen using azacitidine to reverse platinum resistance to carboplatin in patients with platinum resistant or refractory epithelial ovarian cancer. J Clin Oncol (Meeting Abstracts), 26: abstr 3500, 2008.

Bender et al, 1998
Bender, C. M., Pao, M. M., and Jones, P. A. Inhibition of DNA methylation by 5-aza-2'-deoxycytidine suppresses the growth of human tumor cell lines. Cancer Res, 58: 95-101, 1998.

Berry et al 1991
Berry G, Kitchin RM, Mock PA. A comparison of 2 simple hazard ratio estimators based on the logrank test. Stat Med 1991;10(5):749-55.

Bograd et al 2011
Bograd AJ, Suzuki K, Vertes E, Colovos C, Morales EA, Sadelain M, et al. Immune responses and immunotherapeutic interventions in malignant pleural mesothelioma. Cancer Immunol Immunother. 2011;60:1509-27.

Bonomi 2010
Bonomi PD. Implications of key trials in advanced nonsmall cell lung cancer. Cancer 2010;116(5):1155-64.

Braakhuis et al, 1998
Braakhuis, B. J., van Dongen, G. A., van Walsum, M., Leyva, A., and Snow, G. B. Preclinical antitumor activity of 5-aza-2'-deoxycytidine against human and neck cancer xenografts [corrected]. Invest New Drugs, 6: 299-304, 1988.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Brahmer et al 2014
Brahmer JR, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA et al. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis [ASCO abstract 8112]. J Clin Oncol 2014;32(15)(Suppl).

Brusa et al 2013
Brusa D, Serra S, Coscia M, Rossi D, D'Arena G, Laurenti L, et al. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. Haematologica. 2013 Jun; 98(6):953-963.

Burt et al 2011
Burt BM, Rodig SJ, Tilleman TR, Elbardissi AW, Bueno R, Sugarbaker DJ. Circulating and tumor-infiltrating myeloid cells predict survival in human pleural mesothelioma. Cancer. 2011;117(22):5234-44.

Cabrero et al 2015
Cabrero M, Jabbour E, Ravandi F, Bohannan Z, Pierce S, Kantarjian HM, et al. Discontinuation of hypomethylating agent therapy in patients with myelodysplastic syndromes or acute myelogenous leukemia in complete remission or partial response: retrospective analysis of survival after long-term follow-up. Leuk Res. 2015;39(5):520-524.

Chan 2004
Chan AT, Tao Q, Robertson KD, et al. Azacitidine induces demethylation of the Epstein-Barr virus genome in tumors. J Clin Oncol 2004;22:1373-1381.

Ciuleanu et al 2009
Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind, phase 3 study. Lancet 2009;374(9699):1432-40.

Colacino 2013
Colacino JA1, Dolinoy DC, Duffy SA, Sartor MA, Chepeha DB, Bradford CR, McHugh JB, Patel DA, Virani S, Walline HM, Bellile E, Terrell JE, Stoerker JA, Taylor JM, Carey TE, Wolf GT, Rozek LS. Comprehensive analysis of DNA methylation in head and neck squamous cell carcinoma indicates differences by survival and clinicopathologic characteristics. PLoS One. 2013;8(1):e54742.

Collett 2003
Collett D. Modelling survival data in medical research: 2nd ed. Chapman and Hall/CRC; 2003.

DACOGEN®
DACOGEN® (decitabine) for injection, for intravenous use [US prescribing information]. March 2019. Otsuka America Pharmaceutical, Inc., Rockville, MD. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=deb4a13c-855b-4372-9778-6e81da598df6. Accessed 1 May 2019.

DACOGEN®
DACOGEN® [summary of product characteristics]. March 2019. Belgium: Janssen-Cilag International NV. Available at: https://www.medicines.org.uk/emc/medicine/27127. Accessed 26 April 2019.

D'Addario et al 2010
D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(Suppl 5):116-9.

Drake et al 2013
Drake CG, McDermott DF, Sznol M, Choueiri TK, Kluger HM, Powderly JD et al. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up [abstract 4514]. J Clin Oncol 2013;31(Suppl).

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

Ellis et al 2008
Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials 2008;29(4):456-65.

Ferraris et al 2014
Ferraris D, Duvall B, Delahanty G, Mistry B, Alt J, Rojas C, et al. Design, synthesis, and pharmacological evaluation of fluorinated tetrahydrouridine derivatives as inhibitors of cytidine deaminase. J Med Chem. 2014;57(6):2582-2588.

Forde et al 2014
Forde PM, Kelly RJ, Brahmer JR. New strategies in lung cancer: translating immunotherapy into clinical practice. Clin Cancer Res 2014;20(5):1067-73.

Gail and Simon 1985
Gail M, Simon R. Tests for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41(2):361–72.

Garcia-Manero et al 2011
Garcia-Manero G, Gore SD, Cogle C, Ward R, Shi T, MacBeth K, et al. Phase 1 study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. J Clin Oncol. 2011;29(18):2521–2527.

Garcia-Manero et al 2013
Garcia-Manero G, Jabbour E, Borthakur G, Faderl S, Estrov Z, Yang H, et al. Randomized open-label phase II study of decitabine in patients with low- or intermediate-risk myelodysplastic syndromes. J Clin Oncol. 2013;31:2548-2553.

GLOBOCAN 2012
GLOBOCAN. Lung cancer, estimated incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer, World Health Organization; Lyon, 2012. Available at http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed on 16 April 2015.

Gong et al 2009
Gong AY, Zhou R, Hu G, Li X, Splinter PL, O'Hara SP, et al. MicroRNA-513 regulates B7-H1 translation and is involved in IFN-gamma-induced B7-H1 expression in cholangiocytes. J Immunol 2009;182(3):1325-33.

Hamanshi et al 2007
Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of

human ovarian cancer. Proc Nat Acad Sci U S A. 2007;104(9):3360-5.

Herbst et al 2013
Herbst RS, Gordon MS, Fine GD, Sosman JA, Soria JC, Hamid O, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumours [abstract 3000]. J Clin Oncol 2013;31(Suppl 15).

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Hodi et al 2010
Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanan JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published erratum appears in N Engl J Med 2010;363(13):1290]. N Engl J Med 2010;363(8):711-23.

Hodi et al 2010
Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanan JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published erratum appears in N Engl J Med 2010;363(13):1290]. N Engl J Med 2010;363(8):711-23.

Hodi et al 2014
Hodi FS, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial [ASCO abstract 9002]. J Clin Oncol 2014; 32(15)(Suppl).

Howlander et al 2014
Howlander N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. Bethesda (MD): National Cancer Institute,. Available from: URL:http://seer.cancer.gov/csr/1975_2011/ based on November 2013 SEER data submission (posted to the SEER web site, April 2014).

IASLC Staging Manual in Thoracic Oncology
Goldstraw P, ed. Staging manual in thoracic oncology. 7th ed. IASLC 2010. (Available on request)

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumour cells in the escape from host immune system and tumour immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99(19):12293-7.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumour cells in the escape from host immune system and tumour immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99(19):12293-7.

Jabbour et al 2017
Jabbour E, Short NJ, Montalban-Bravo G, Huang X, Bueso-Ramos C, Qiao W, et al. Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. Blood. 2017; 130:1514-1522.

Juergens et al 2011
Juergens RA, Wrangle J, Vendetti FP, Murphy SC, Zhao M, Coleman B, Sebree R, Rodgers K, Hooker CM, Franco N, Lee B, Tsai S, Delgado IE, Rudek MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM. Combination epigenetic therapy has efficacy in patients with refractory advanced non small cell lung cancer. Cancer Discov 2011 December; 1(7):598-607.

Karon et al 1973
Karon, M., Sieger, L., Leimbrock, S., Finklestein, J. Z., Nesbit, M. E., and Swaney, J. J. 5-Azacytidine: a new active agent for the treatment of acute leukemia. Blood, 42: 359-365, 1973.

Keir et al 2008
Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.

Kenney 2014
Kenney SC, Mertz JE. Regulation of the latent-lytic switch in Epstein-Barr virus. Semin Cancer Biol 2014;26:60-68. Available at: http://dx.doi.org/10.1016/j.semcancer.2014.01.002.

Kirkwood et al 2010
Kirkwood JM, Lorigan P, Hersey P, Hauschild A, Robert C, McDermott D, et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. Clin Cancer Res 2010;16(3):1042-8.

Kitano et al 2014
Kitano S, Postow MA, Ziegler CG, Kuk D, Panageas KS, Cortez C, et al. Computational algorithm-driven evaluation of monocytic myeloid-derived suppressor cell frequency for prediction of clinical outcomes. Cancer Immunol Res 2014;2(8):812-21.

Klein et al 2007
Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007;26(24):4505-19.

Korn et al 2008
Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008;26(4):527-34.

Krambeck et al 2007
Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. Clin Cancer Res. 2007;13(6):1749-56.

Kresowik and Griffith 2009
Kresowik TP, Griffith TS. Bacillus Calmette–Guerin immunotherapy for urothelial carcinoma of the bladder. Immunother. 2009;1(2):281-8.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70(3):659-63.

Liao et al 2012
Liao YM, Mirshahidi H, Zhang K, Mirshahidi S, Williamson S, Hsueh CT. Abstract 2663: Phase I study of azacitidine and cisplatin in patients with advanced head and neck or non-small cell lung cancer. AACR 103rd Annual Meeting 2012, Mar 31-April 4, 2012, Chicago, IL

Lo 2013
Lo KW, Chung GTY, To KF, et al. Acquired genetic and epigenetic alterations in nasopharyngeal carcinoma. In: Busson P, ed. Nasopharyngeal Carcinoma. New York, NY:Springer New York;2013:61-81.

Loos et al 2008
Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic adenocarcinoma. Cancer

Lett. 2008;268(1):98-109.

Lyko et al, 2005
Lyko, F. and Brown, R. DNA methyltransferase inhibitors and the development of epigenetic cancer therapies. J Natl Cancer Inst, 97: 1498-1506, 2005.

Marcucci et al, 2005
Marcucci, G., Silverman, L., Eller, M., Lintz, L., and Beach, C. L. Bioavailability of azacitidine subcutaneous versus intravenous in patients with the myelodysplastic syndromes. J Clin Pharmacol, 45: 597-602, 2005.

McDermott 2009
McDermott DF. Immunotherapy of metastatic renal cell carcinoma. Cancer. 2009;115(10 suppl):2298–305.

Meyer et al 2014
Meyer C, Cagnon L, Costa-Nunes Cm, Baumgaaertner P, Montandon N, Leyvraz L, et al. Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab. Cancer Immunol Immunother 2014;63(3):247-57.

Miranda 2007
Miranda MB, Jones PA. DNA methylation: the nuts and bolts of repression. J Cell Physiol 2007;213:384-390.

Mu et al 2011
Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011 Sep;28(3):682-8.

Mu et al 2011
Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumour cells immune escape through suppressing tumour infiltrating dendritic cells maturation. Med Oncol 2011;28(3):682-8.

Nakano et al 2001
Nakano O, Sato M, Naito Y, Suzuki K, Orikasa S, Aizawa M, et al. Proliferative activity of intratumoral $CD8^+$ T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. Cancer Res. 2001;61:5132-6.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ (2013) Population Pharmacokinetics of Sifalimumab, an Investigational Anti-Interferonalpha Monoclonal Antibody, in Systemic Lupus Erythematosus. Clin Pharmacokinet 52:1017–1027

Ng et al 2006
Ng CM, Lum BL, Gimenez V, et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275–84.

NCCN 2014
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 4.2014. www.nccn.org.

NIOSH
NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2004-165.

Nishino et al 2013
Nishino M, Biobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19(14):3936-43.

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an anti-tumour effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

OSHA
OSHA technical manual. TED 1-0.15A. Section VI: Chapter 2. Controlling OccupationalExposure to Hazardous Drugs. OSHA. [webpage]. 1999. Available from: http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252-64.

Park et al 2011
Park IS, Chang X, Loyo M, Wu G, Chuang A, Kim MS, Chae YK, Lyford-Pike S, Westra WH, Saunders JR, Sidransky D, Pai SI. Characterization of the methylation patterns in human

papillomavirus type 16 viral DNA in head and neck cancers. Cancer Prev Res 2011 Feb;4(2):207-17.

Paz-Ares et al 2013
Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31(23):2895-902.

Peggs et al 2009
Peggs KS, Quezada SA, Allison JP. Cancer immunotherapy: co-stimulatory agonists and coinhibitory antagonists. Clin Exp Immunol 2009;157:9-19.

Pisters and LeChevalier 2005
Pisters KM, LeChevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol 2005;23(14):3270-8.

Polovich 2005
Polovich M, White JM, Kelleher LO (eds.). Chemotherapy and biotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh (PA): Oncology Nursing Society;2005.

Plumb et al, 2000
Plumb, J. A., Strathdee, G., Sludden, J., Kaye, S. B., and Brown, R. Reversal of drug resistance in human tumor xenografts by 2'-deoxy-5-azacytidine-induced demethylation of the hMLH1 gene promoter. Cancer Res, 60: 6039-6044, 2000.

Reck et al 2014
Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii27-39.

Ribas et al 2013
Ribas A, Kefford R, Marshall MA, Punt CJA, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013;31:616-22.

Sandler et al 2006
Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355(24):2524-50.

Santini et al, 2001

Santini, V., Kantarjian, H. M., and Issa, J. P. Changes in DNA methylation in neoplasia: pathophysiology and therapeutic implications. Ann Intern Med, 134: 573-586, 2001.

Scagliotti et al 2008
Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21)3543-51.

Schadendorf et al 2013
Schadendorf D, Hodi FS, Robert C et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma. Presented at: European Cancer Congress 2013 (ECCO-ESMO-ESTRO); September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract 24.

Schiller et al 2002
Schiller JH, Harringdon D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;10(346):92-8.

Schwartsmann et al, 2000
Schwartsmann, G., Schunemann, H., Gorini, C. N., Filho, A. F., Garbino, C., Sabini, G., Muse, I., DiLeone, L., and Mans, D. R. A phase I trial of cisplatin plus decitabine, a new DNA-hypomethylating agent, in patients with advanced solid tumors and a follow-up early phase II evaluation in patients with inoperable non-small cell lung cancer. Invest New Drugs, 18: 83-91, 2000.

Schwarzenbach et al 2014
Schwarzenbach H, Nishida N, Calin GA, Pantel K. Clinical evidence of circulating cell-free microRNAs in cancer. Nat Rev Clin Oncol 2014;11(3):145-56.

Segal NH et al 2015
Segal NH, Ou SHI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, Weiss J, Schoffski P, Antonia SJ, Massard C, Zandberg DP, Khleif SN, Li X, Rebelatto MC, Steele KE, Robbins PB, Blake-Haskins JA, Butler MO. Safety and efficacy of MEDI4736, an Anti-PD-L1 Antibody, in Patients from a Squamous Cell Carcinoma of the Head and Neck (SCCHN) Expansion Cohort. ASCO abstract 2015.

Seiwert et al 2014
Seiwert TY, Burfness B, Weiss J, Gluck I, Eder JP, Pai SI, et al. A phase Ib study of MK- 3475 in patients with human papillomavirus (HPV)-associated and non-HPV- associated head and neck (H/N) cancer. J Clin Oncol 2014;32(5s):6011.

Selke and Siegmund 1983
Selke T, Siegmund D. Sequential analysis of the proportional hazards model. Biometrika 1983;70:315-26.

Shin and Khuri 2013
Shin DM, Khuri FR. Advances in the management of recurrent or metastatic squamous cell carcinoma of the head and neck. Head Neck 2013;35(3):443-53.

Silverman et al, 2002
Silverman, L. R., Demakos, E. P., Peterson, B. L., Kornblith, A. B., Holland, J. C., Odchimar-Reissig, R., Stone, R. M., Nelson, D., Powell, B. L., DeCastro, C. M., Ellerton, J., Larson, R. A., Schiffer, C. A., and Holland, J. F. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol, 20: 2429-2440, 2002.

Soengas et al, 2001
Soengas, M. S., Capodieci, P., Polsky, D., Mora, J., Esteller, M., Opitz-Araya, X., McCombie, R., Herman, J. G., Gerald, W. L., Lazebnik, Y. A., Cordon-Cardo, C., and Lowe, S. W. Inactivation of the apoptosis effector Apaf-1 in malignant melanoma. Nature, 409: 207-211, 2001.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's Method with the conventional approach for interval-censored data analysis. Stat Biopharm Res 2010;2(1):97-108.

Tarhini 2013
Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica 2013;857519. Epub 2013 Apr 17.

Tarhini and Kirkwood 2008
Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008;8(10):1583-93.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-54.

Topalian et al 2014
Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol, 2014 Apr 1; 32(10):1020-30.

Velicescu et al, 2002
Velicescu, M., Weisenberger, D. J., Gonzales, F. A., Tsai, Y. C., Nguyen, C. T., and Jones, P. A. Cell division is required for de novo methylation of CpG islands in bladder cancer cells. Cancer Res, 62: 2378-2384, 2002.

Vermoken 2013
Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359(11):1116-27.

Von Hoff 1976
Von Hoff, D. D., Slavik, M., and Muggia, F. M. 5-Azacytidine. A new anticancer drug with effectiveness in acute myelogenous leukemia. Ann Intern Med, 85: 237-245, 1976.

Wang et al 2009
Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012–24.

Wang et al 2013
Wang Z, Han J, Cui Y, Fan K, Zhou X. Circulating microRNA-21 as noninvasive predictive biomarker for response in cancer immunotherapy. Med Hypotheses 2013;81(1):41-3.

Wang et al 2014
Wang E, Kang D, et al. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol. 2014 Oct; 54(10):1108-16.

Weber et al 2012
Weber J, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30(21):2691-7.

Weiss et al, 1977
Weiss, A. J., Metter, G. E., Nealon, T. F., Keanan, J. P., Ramirez, G., Swaiminathan, A., Fletcher, W. S., Moss, S. E., and Manthei, R. W. Phase II study of 5-azacytidine in solid tumors. Cancer Treat Rep, 61: 55-58, 1977.

Whitehead and Whitehead 1991
Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991;10(11):1665-77.

Wolchok et al 2013
Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369(2):122-33.

Yuan et al 2011
Yuan J, Adamow M, Ginsberg BA, Rasalan TS, Ritter E, Gallardo HF, et al. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlated with clinical benefit in advanced melanoma patients treated with ipilimumab. Proc Natl Acad Sci USA 2011;108(40):16723-8.

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Anti-tumour immunotherapy by blockade of the

Zhang et al 2012
Zhang S, Shi R, Li C, et al. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18–28.

Zhang 2012b
Zhang X, Li W, Li H, et al. Genomic methylation profiling combined with gene expression microarray reveals the aberrant methylation mechanism involved in nasopharyngeal carcinoma taxol resistance. Anticancer Drugs 2012b;23:856-864.

US DHHS
U.S. Department of Health and Human Services. Public Health Service, National Institutes of Health; 1999.

Appendix 1: Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

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 (unless indicated otherwise). 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** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE 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.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – 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. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., 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 (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to

Appendix 1: Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
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. Note: For asymptomatic amylase or lipase levels of >2.0×ULN, 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: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., 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.

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

Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** of the start of the immune-mediated event	− All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. − The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. − The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. − For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. − With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (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 consults.
	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 (e.g., 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 methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue 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 consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., 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 (e.g., 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 patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**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). – When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Patients should be thoroughly evaluated to rule out any

		alternative etiology (e.g., 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, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical intervention indicated*)	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 be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 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 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

	* "medical intervention" is not invasive		– Consider, as necessary, discussing with 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** 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 (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	*This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective		
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal	• No dose modifications. • If it worsens, then treat as described for elevations in the row below.	– Continue LFT monitoring per protocol.
	AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. • If toxicity worsens, then treat as described for elevation in the row below. • If toxicity improves to AST or ALT	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing 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 work up and start prompt treatment with IV

	normal, >1.5-3.0×baseline if baseline abnormal	≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, resume study drug/study regimen after completion of steroid taper.	methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal	For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days For elevations in transaminases >8×ULN or elevations in TB >5×ULN if baseline normal, or for elevations in transaminases	– 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 (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

		>8×baseline and/or TB >5×baseline if baseline abnormal, permanently 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 (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN,	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row	

DILI/liver decompensation	**whether normal or elevated at baseline**	below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose untilresolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to 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 treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of

	≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate 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).[a]
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**

If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):

- **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase riseFor example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)**
- **For the third and fourth levels of transaminase rises, 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 (e.g., 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 (e.g., 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.

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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – 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	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

	6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)		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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**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 IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing 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 permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of	**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:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – 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, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections).

amylase/lipase increased also included in this section)			– Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., 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. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – 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 consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, 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.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and

	Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) 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.	without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) 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 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current

			NCCN guidelines for treatment of cancer-related infections).[a]
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 (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. –

	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:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., 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 (e.g., 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 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre	**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

and myasthenia gravis)		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 (e.g., 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 Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – 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 started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing 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.
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:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin 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. o 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:* 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.
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 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They 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.

		For Grade 4: Permanently discontinue study drug/study regimen.	○ 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. *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.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1	No dose modifications required unless	**For Grade 1 (no definitive findings):**

(asymptomatic with laboratory [e.g., BNP] or cardiac imaging abnormalities)	clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	- Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.

	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** − Monitor symptoms daily, hospitalize. − Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. − Supportive care (e.g., oxygen). − If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** − Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. − If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis;

		refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue

		additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[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; imAE immune-mediated 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; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

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 (e.g., 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 (e.g., 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 (e.g., 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.

Non–Immune-Mediated Reactions

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 (i.e., 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.

Appendix 2 Schedule of study procedures: follow-up for subjects who have completed azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736) and tremelimumab combination treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), or tremelimumab due to toxicity in the absence of confirmed progression of disease

Evaluation	Time Since Last Dose of Study Treatment							
	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							
Urine hCG or serum βhCG	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status	X	X	X		X (and month 9)			X
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					X
Serum chemistry	X	X	X					

Appendix 2 Schedule of study procedures: follow-up for subjects who have completed azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736) and tremelimumab combination treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), or tremelimumab due to toxicity in the absence of confirmed progression of disease

Evaluation	Time Since Last Dose of Study Treatment							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Thyroid function tests (TSH, and fT3 and fT4)[b]	X							
Tumor biopsy	~~X~~							
Peripheral blood	~~X~~							
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. For subjects who **discontinue MEDI4736 due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks (per Schedule of Assessments), then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Assessments for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).							

[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.

Appendix 3 Schedule of study procedures: follow-up for subjects who have discontinue azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), and tremelimumab combination treatment due to confirmed progression of disease at the investigator discretion

Evaluation	Time Since Last Dose of Study Treatment							
	Day (±3)	Months (± 30 days)						12 Months and Every 6 Months (± 30 days)
	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					
Concomitant medications	X		X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status[b]	X		X					
Subsequent anti-cancer therapy	X		X		X			X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted			X		X			X (every 3 months)
Urine hCG or serum βhCG	X							
Hematology	X		X					
Serum chemistry	X		X					
Thyroid function tests (TSH, and fT3 and fT4)[c]	X							
Tumor Biopsy	~~X~~							

Appendix 3 Schedule of study procedures: follow-up for subjects who have discontinue azacitidine or oral decitabine (ASTX727), durvalumab (MEDI4736), and tremelimumab combination treatment due to confirmed progression of disease at the investigator discretion

Evaluation	Time Since Last Dose of Study Treatment							
	Day (±3)	Months (± 30 days)						12 Months and Every 6 Months (± 30 days)
	30	2	3	4	6	8	10	
PBMCs	X							
Tumour assessment (CT or MRI)	For subjects who **continue on MEDI4736 post-confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of **first infusion**until MEDI4736 is stopped. For subjects who **discontinue MEDI4736 following confirmed progression**, **scans should be conducted according to local clinical practice** and submitted for central review until a new treatment is started (these scans are optional).							

[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.

Appendix 4. Durvalumab (MEDI4736) DOSE CALCULATIONS

For durvalumab (MEDI4736) dosing done depending on subject weight:

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 (MEDI4736) nominal concentration.

The corresponding volume of durvalumab (MEDI4736) should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are 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) / 10.0 (mL/vial)

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 300 mg = 10 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 300 mg / 50 (mg/mL) = 6.0 mL

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

Number of vials = 6.0 (mL) / 10.0 (mL/vial) = 1 vials

Appendix 5. Durvalumab (MEDI4736) DOSE VOLUME CALCULATIONS

For durvalumab (MEDI4736) flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 50 (mg/mL)

where 50 mg/mL is durvalumab (MEDI4736) nominal concentration.

The corresponding volume of durvalumab (MEDI4736) should be rounded to the nearest tenth mL (0.1 mL).

3. 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) / 10.0 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000 / 50 (mg/mL) = 30.0 mL

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

Number of vials = 30.0 (mL) / 10.0 (mL/vial) = 3 vials

Appendix 6. Tremelimumab DOSE CALCULATIONS

For tremelimumab dosing done depending on subject weight:

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 / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are 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) / 20.0 (mL/vial)

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 30 mg = 1 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 30 mg / 20 (mg/mL) = 1.5 mL

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

Number of vials = 1.5 (mL) / 20.0 (mL/vial) = 1 vials

Appendix 7. Tremelimumab DOSE VOLUME CALCULATIONS

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).

3. 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) / 20 (mL/vial)

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

Dose (mL) = 75 mg / 20 (mg/mL) = 3.8 mL

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

Number of vials = 3.8 (mL) / 20 (mL/vial) = 1 vial