| LUDWIG CANCER RESEARCH | **Study Protocol** | **LUD2014-011** | **US-IND# 130529** |
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| | **Amendment 6.0** | **Final** | **02-NOV-2021** |

| **Protocol Title** |
|---|
| A Phase 1/2 Study of In Situ Vaccination with Tremelimumab and IV Durvalumab (MEDI4736) Plus the Toll-like Receptor Agonist PolyICLC in Subjects with Advanced, Measurable, Biopsy-accessible Cancers |

**Objectives and Synopsis**

This is an open-label, multicenter, Phase 1/2 study of the CTLA-4 antibody, tremelimumab, and the PD-L1 antibody, durvalumab (MEDI4736), in combination with the tumor microenvironment (TME) modulator polyICLC, a TLR3 agonist, in subjects with advanced, measurable, biopsy-accessible cancers. Subjects will receive intratumoral and intramuscular (IM) administration of polyICLC and intravenous (IV) administration of durvalumab, together with either IV or intratumoral administration of tremelimumab. The study will be conducted in 2 phases.

**Phase 1 Cohorts:** There will be enrollment to 3 subject cohorts in Phase 1, with staggered initiation of enrollment.

- Cohort 1A: IV Durvalumab+ intratumoral/IM polyICLC. After safety is demonstrated in the first 3-6 subjects in Cohort 1A, Cohorts 1B and 1C will open to enrollment.
- Cohort 1B: IV Durvalumab + IV Tremelimumab + intratumoral/IM polyICLC.
- Cohort 1C: IV Durvalumab + intratumoral Tremelimumab + intratumoral/IM polyICLC.

Dose de-escalations for determination of the recommended combination doses (RCDs) through the assessment of dose-limiting toxicities (DLTs) will be performed based on the dose levels in the table below and respective standard 3 + 3 rules.

| **Cohort 1A** | | | |
|---|---|---|---|
| **Dose Level** | **Durvalumab Q4W (IV)** | **PolyICLC (ITM/IM)** | |
| -1 | 750 mg | 1 mg | |
| ***0 (Starting Level)*** | ***1500 mg*** | ***1 mg*** | |
| **Cohort 1B** | | | |
| **Dose Level** | **Durvalumab Q4W (IV)** | **PolyICLC (ITM/IM)** | **Tremelimumab Q4W (IV)** |
| -1 | RCD from Cohort 1A | 1 mg | 22.5 mg |
| ***0 (Starting Level)*** | ***RCD from Cohort 1A*** | ***1 mg*** | ***75 mg*** |
| **Cohort 1C** | | | |
| **Dose Level** | **Durvalumab Q4W (IV)** | **PolyICLC (ITM/IM)** | **Tremelimumab (ITM)** |
| -1 | RCD from Cohort 1A | 1 mg | 3 mg |
| ***0 (Starting Level)*** | ***RCD from Cohort 1A*** | ***1 mg*** | ***10 mg*** |
| Q4W = every 4 weeks; IV = intravenous; ITM = intratumoral; IM= intramuscular<br>Note: See Section 3.1.7.1 for durvalumab doses for instances when a subject's body weight drops to ≤ 30 kg while on the study. | | | |

The *primary objective* of Phase 1 is to determine the RCDs of the dosing regimen, based on assessment of toxicity and tolerability. The *secondary objective* is to obtain preliminary evidence of clinical efficacy as measured by objective response rate (ORR) by irRECIST and RECIST 1.1, progression-free survival (PFS), and overall survival (OS).

**Phase 2 Cohort**: Upon determination of the RCD in Cohort 1C, up to 66 evaluable subjects will be treated in Cohort 2. If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2. The *primary objective* for Phase 2 is the evaluation of clinical efficacy as measured by ORR, PFS, and OS.

**All Cohorts:** *Secondary objectives* are the evaluation of safety and tolerability. An *exploratory objective* is to evaluate the biological activity, including effects on the TME and immunological responses. Assessment methods include CTCAE V4.03 for safety and irRECIST and RECIST 1.1 for clinical efficacy.

**Per Amendment 6.0:**

All subjects have completed treatment, and by the date of implementation of this amendment, all subjects will have completed On Study Follow-up. This amendment provides that the Post Study Follow-up for the collection of survival data will be discontinued as of 28 February 2022, and the study will be completed.

| **Sponsor: Ludwig Institute for Cancer Research, New York, NY** | |
|---|---|
| **Sponsor:**<br>Ludwig Institute for Cancer Research, Ltd. | **Study Chairs:**<br>[redacted] Tisch Cancer Institute Icahn School of Medicine at Mount Sinai |
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# 1 Background

## 1.1 Biopsy-accessible Advanced, Measurable Cancers

The eligible disease types for this study were selected for inclusion based either on their ability to be accessed through biopsy (as defined in Section 5.1) and/or on their viral etiologies (i.e., non-viral-associated head and neck squamous cell carcinoma [HNSCC] and Merkel cell carcinoma [MCC]).

### 1.1.1 Head and Neck Squamous Cell Carcinoma

The incidence of HNSCC is 45,000 cases per year, with a mortality of > 12,000 subjects per year. While viral-associated HNSCC is associated with 80% overall survival (OS) following treatment, recurrence rates remain high in non-viral-associated HNSCC, despite treatment with surgical resection, chemotherapy, and radiation. Up to 50% of non-viral-associated cases may present with advanced disease, in which the likelihood of complete resection decreases. Subjects with unresectable tumors have been selected for eligibility in this study because of the accessibility of the lesions, indications of some responses to immunotherapy, and usual progression and regional disfigurement despite treatment with chemotherapy.

### 1.1.2 Locally Recurrent Breast Cancer

Carcinomas of the breast are often cured with surgical management, and metastatic breast cancer has a high rate of clinical response with hormonal therapy, cytotoxic chemotherapy, and/or trastuzumab. However, a subset of patients develops recurrent breast cancer locally on the chest wall, which is accessible for biopsy, and may include skin, subcutaneous, or nodal metastases alone or in addition to systemic disease. Especially among patients with local recurrence within 2 years of breast-conserving surgery, the probability of survival is less than 10%.(1)

### 1.1.3 Sarcoma

Sarcomas are uncommon malignancies arising from soft tissues and are found most commonly in either retroperitoneal or extremity sites. Sarcomas, particularly in the extremities, are prone to local recurrence, and can be challenging to manage, as they do not respond well to most systemic therapies. Sarcomas available for biopsy and injection may be eligible for this study.

### 1.1.4 Merkel Cell Carcinoma

MCC is a malignancy arising from Merkel cells in the skin, which can be aggressive and unresponsive to systemic therapy. MCC is responsive to radiation therapy, but systemic metastases are often lethal. Approximately 80% of MCCs are linked etiologically to the Merkel cell polyomavirus (MCV).(2, 3) MCC arises on the skin and often metastasizes to regional or distant skin sites.

### 1.1.5 Cutaneous T-cell Lymphoma

The cutaneous T-cell lymphomas (CTCLs) comprise a heterogeneous group of T-cell lymphoproliferative disorders such as mycosis fungoides and Sézary syndromes. Patients with advanced-stage disease with significant nodal, visceral, or blood involvement can be treated with biologic-response modifiers, HDAC inhibitors, and/or chemotherapy. Patients refractory to

treatment have responded to intratumoral CpG treatment, suggesting that TLR agonists may benefit these patients.(4)

### 1.1.6 Metastatic Melanoma

Until recently, darcarbazine (DTIC) and high-dose IL-2 were the only agents approved for use in the United States (US) for the treatment of metastatic melanoma. Durable responses to high-dose IL-2 occur in a small subset of responding patients, although administration of high-dose IL-2 requires hospitalization and can induce severe toxicities, which limits the utilization of this agent. Over the past few years, targeted therapies interfering with BRAF and MEK signaling have been approved by the FDA for patients with BRAF-mutant melanoma, and the CTLA-4 antibody ipilimumab (Yervoy®) and PD-1 antibodies pembrolizumab (Keytruda®) and nivolumab (Opdivo®) have been approved for the treatment of metastatic melanoma. Benefits of high-dose IL-2, ipilimumab, and PD1 antibodies are mediated directly or indirectly through T-cell activation; thus, they are proof-of-principle for the ability of T-cell-directed therapies to control melanoma. However, some patients will fail or be ineligible for all of these therapies. Melanoma often metastasizes to distant skin and regional sites, which are accessible for intralesional therapy and biopsies, and there have been reports of responses to topical TLR agonists (imiquimod) and intralesional therapies (IL-2, BCG, and talimogene laherparepvec).

### 1.1.7 Genitourinary Cancers with Accessible Metastases (Bladder, Renal, Prostate)

Breakthrough status has recently been given for anti-PD-L1 agents in advanced bladder cancers, and checkpoint blockade inhibition with other monoclonal antibodies is being actively tested in genitourinary (GU) cancers. Tumor infiltration with T cells and responsiveness to therapies such as IL-2 in a limited set of renal cancer patients support the concept that enhancing immunity locally may have effects in the TME. Since these cancers are accessible for intralesional injection and biopsy, patients who are refractory to other therapies, including checkpoint blockade inhibitors, would be eligible for treatment.

## 1.2 Toll-like Receptor: PolyICLC

The toll-like receptors (TLRs) are a family of pathogen recognition receptors expressed broadly on hematopoietic cells (e.g., myeloid dendritic cells [mDC], plasmacytoid [pDC], monocytes, and B cells) that recognize pathogen-associated molecular patterns (PAMPs), activate innate immune responses, and facilitate the development of adaptive responses. The engagement of specific TLRs leads to the activation of different cell populations and the production of distinct patterns of cytokines and other inflammatory mediators, resulting in alternative immune response profiles.

Polyinosinic-polycytidylic acid (polyIC) is a double-stranded RNA (dsRNA) that acts as a TLR3 agonist. However, its short half-life limits its usefulness. To increase half-life and its practical use in the clinical setting, polyIC has been stabilized with polylysine and carboxymethylcellulose as polyICLC (Hiltonol®, Oncovir Inc.). Like polyIC, polyICLC is a TLR3 agonist. TLR3 is expressed in the early endosome of myeloid DC; thus polyICLC preferentially activates myeloid dendritic cells, favoring a Th1 cytotoxic T-cell response.(5, 6) PolyICLC also activates natural killer (NK) cells and induces cytolytic potential.(6) It has been administered intratumorally in a sarcoma patient with dramatic clinical tumor regression.(7) A clinical trial further testing intratumoral polyICLC is underway (NCT02423863).

PolyICLC is provided as a clinical grade reagent for experimental use in single-use vials containing 1 mL of approximately 2 mg/mL solution under contract from Oncovir to the Ludwig Institute for Cancer Research and the Cancer Vaccine Consortium.

PolyICLC has been used safely in cancer patients, with intravenous (IV) doses up to 300 µg/kg.(4) In this study, 1 mg of polyICLC will be administered per dose, as used in other trials (e.g., NCT01008527 and NCT01984892) and as administered intratumorally with clinical benefit (7) (e.g., NCT02423863).

## 1.3 CTLA-4 Antibody: Tremelimumab

CTLA-4 (CD152) is constitutively expressed by T lymphocytes within the cytoplasm but is expressed at the cell surface upon antigen activation. Its ligation on CD80 or CD86 down regulates the stimulatory signal of the T-cell receptor. Blockade of CTLA-4 abrogates this negative signal, supporting T-cell activation and expansion. Therapeutic blockade of CTLA-4 in murine models and in humans can lead to durable objective regressions of metastatic cancer. The mechanism also may be mediated in part by depletion of regulatory T cells. One CTLA-4 blocking antibody (ipilimumab) has been approved by the FDA for therapy of advanced melanoma. The CTLA-4 blocking antibody in the present study (tremelimumab) has similar clinical activity but has not yet been approved for use in humans.

Tremelimumab is briefly described in this section below. Refer to the current Investigator's Brochure for complete and current information.

Tremelimumab is a human immunoglobulin (Ig)G2 monoclonal antibody (mAb) being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; CD152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation.

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects participating in 10 of the 22 clinical studies, 2 of which are ongoing. An additional 497 subjects have received tremelimumab or placebo in the ongoing double-blinded, Phase 2b mesothelioma study, D4880C00003 (DETERMINE; data remain blinded). Tremelimumab in combination with other anticancer agents has been administered to 208 subjects with a variety of tumor types in 12 of the 22 clinical studies, 7 of which are ongoing.

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following IV infusion.

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this mechanism of action. In general, tumor response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumors such as refractory metastatic melanoma. Some subjects may have what is perceived to be progression of their disease in advance of developing disease

stabilization or a tumor response. Overall, the impact on conventionally-defined progression-free survival (PFS) can be small; however, the durable response or stable disease seen in a proportion of subjects can lead to significant prolongation of overall survival (OS).

Ipilimumab was shown to significantly improve OS in both first- and second-line treatment of subjects with metastatic melanoma. The melanoma data with ipilimumab clearly demonstrate that a small proportion of subjects with an objective response had significant prolongation of OS, supporting the development of this class of agents in other tumors. Although Phase 2 and Phase 3 studies of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma.(8, 9) In a large Phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in subjects with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for TIC/temozolomide (HR = 1.1416, p = 0.1272).(9)

The profile of adverse events (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 subjects with melanoma). As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), AEs (all grades, regardless of causality) reported in > 10% of subjects in the completed and rollover tremelimumab monotherapy studies (N = 973, integrated data) were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.8%), pruritus (27.3%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.2%). Based on integrated data from completed studies of tremelimumab in combination with other agents (N = 116), AEs (all grades, regardless of causality) reported in > 15% of subjects were diarrhea (54.3%); nausea (40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations. The events of diarrhea, rash, and pruritus are considered identified risks of tremelimumab. Acute renal failure was reported in subjects who received the combination of tremelimumab and sunitinib; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by following current guidelines for the management of immune-related toxicities.

Clinical studies of tremelimumab are ongoing in several solid tumor types, including malignant mesothelioma, hepatocellular carcinoma (HCC), and non-small-cell lung cancer (NSCLC).

## 1.4 PD-L1 Antibody: Durvalumab (MEDI4736)

Programmed death-1 (PD-1, CD279) is a member of the immunoglobulin superfamily (IGSF) of molecules involved in regulation of T cell activation. PD-1 acquired its name ‘programmed death’ when it was identified in 1992 as a gene upregulated in T cell hybridoma undergoing cell death.(10) The structure of PD-1 is composed of 1 IGSF domain, a transmembrane domain, and an intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM)

and an immunoreceptor tyrosine-based switch motif (ITSM).(11-13) PD-1 has 2 binding partners: PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273), distant relatives of the B7-1 and B7-2 molecules. PD-L1, discovered in 1999, is expressed quite broadly, on both hematopoietic and non-hematopoietic lineages.(14-16) It is found on T cells, B cells, macrophages, NK cells, DCs, and mast cells.(17) It has also been described on peripheral tissues including cardiac endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types.(17-28) PD-L1 is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells.(29) Regulation of PD-L1 is mediated, in part, by type I and type II interferons. PD-L2 was identified in 2001.(30, 31) Its expression is far more restricted and is confined largely to hematopoietic cells.(32) However, PD-L2 is expressed on some pulmonary epithelial cells and its expression may be increased by pulmonary viral infections or interferon-gamma.(33)

Engagement of PD-1 on T cells inhibits activation, with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T cell function.(34-38) Inhibitory signaling by PD-1 is thought to depend upon the cytosolic ITSM domain, which associates with phosphatases SHP-1 and SHP-2.(39, 40)

Durvalumab is briefly described in this section below. Refer to the current Investigator's Brochure (IB) for complete and current information.

Durvalumab is a human immunoglobulin G1 kappa monoclonal antibody (MAb) directed against human PD-L1. Durvalumab has an overall molecular weight of approximately 149 kDa, including N-linked oligosaccharides. The antibody is composed of 2 identical heavy chains of approximately 49,670 Da each, and 2 identical light chains of approximately 23,390 Da each. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcm receptors, responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC).(41) Subsequent to this triple mutation, the anticipated lack of durvalumab-mediated ADCC and complement-dependent cytotoxicity were confirmed using cell based functional assays. Durvalumab is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and cluster of differentiation (CD) 80 receptors.

As of the data cutoff dates in the IB (15Apr2015 to 12Jul2015), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored (6 monotherapy and 14 combination therapy) and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy.

These events are manageable by available/established treatment guidelines as described in the study protocols.

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies.

# 2 Study Rationale

Recent studies indicate that local (intratumoral) delivery of monoclonal antibodies (including anti-CTLA-4 therapy) in mice stimulates equivalent immune responses while limiting the autoimmune toxicity often observed with systemic administration of these agents.(42, 43) An ongoing clinical study of intratumoral ipilimumab plus intratumoral SD-101 (a toll-like receptor 9 agonist) and local radiation is currently investigating the safety and efficacy of this technique in subjects with low-grade B-cell lymphomas (ClinicalTrials.gov identifier NCT02254772).

The current study will implement intratumoral administration of tremelimumab, and hypothesizes that (1) the combination of intratumoral and systemic therapy with checkpoint blockade agents and polyICLC will be safe, (2) the combination of intratumoral and systemic therapy will induce clinical tumor responses in cancers that do not respond well to systemic checkpoint blockade alone, (3) the combination regimen will induce systemic antitumor T-cell and antibody responses, including responses to autologous tumor antigens, and (4) the combination regimen will induce immune signatures in the treated tumors, with upregulation of IFNγ, PD-L1 expression, T-cell recruiting chemokines, and T-cell infiltrates.

According to Medimmune, the combination dose selection of 1 mg/kg Q4W for tremelimumab and 20 mg/kg Q4W for durvalumab was based on the identification of an optimal dose of durvalumab that would "yield sustained target suppression, optimize synergy of the combination, while maintaining the balance of safety in combination with tremelimumab." This is consistent with the dosing regimen to be evaluated in the Medimmune program going forward.

The fixed dosing is based on information from Medimmune, which indicates that the dose and schedule of 1500 mg durvalumab Q4W and 75 mg tremelimumab Q4W was selected based on PK models as described below.

Using population PK models, simulations indicated that both body weight-based and fixed dosing regimens of durvalumab and tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimens. A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, Medimmune considers it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab is equivalent to 10 mg/kg Q2W, 1500 mg Q4W durvalumab is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

The 1500 mg Q4W dosing of durvalumab is recommended only for subjects with > 30 kg body weight in order to limit endotoxin exposure. See Section 3.1.7.1 for details regarding durvalumab dose requirements for instances when a subject's body weight drops to ≤ 30 kg while on the study.

See Section 3.1.7.1 for additional details regarding the dose de-escalation cohorts for durvalumab and tremelimumab.

# 3 Experimental Plan

## 3.1 Study Design

This is an open-label, multicenter, Phase 1/2 study to evaluate the CTLA-4 antibody, tremelimumab, and the PD-L1 antibody, durvalumab, in combination with the tumor microenvironment (TME) modulator polyICLC, a TLR3 agonist, in subjects with advanced, measurable, biopsy-accessible cancers (as defined in Section 5.1).

Subjects will receive intratumoral and intramuscular (IM) administration of polyICLC and intravenous (IV) administration of durvalumab, together with either IV or intratumoral administration of tremelimumab. The study will be conducted in 2 phases. There will be enrollment to 3 subject cohorts in Phase 1, as described in Section 3.1.2.

Dose de-escalations for determination of the recommended combination doses (RCDs) through the assessment of dose-limiting toxicities (DLTs) will be performed based on the available dose levels and respective standard 3 + 3 rules.

Once determined, the RCD of the dosing regimen will then be expanded in the Phase 2 portion of the study. If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2.

### 3.1.1 Study Phase

Phase 1/2

### 3.1.2 Enrollment/Randomization

For Phase 1 of the study, there will be enrollment to 3 subject cohorts, with staggered initiation of enrollment:

- Cohort 1A: IV Durvalumab + intratumoral/IM polyICLC.
- Cohort 1B: IV Durvalumab + IV Tremelimumab + intratumoral/IM polyICLC.
- Cohort 1C: IV Durvalumab + intratumoral Tremelimumab + intratumoral/IM polyICLC.

After safety is demonstrated in the first 3-6 subjects in Cohort 1A, Cohorts 1B and 1C will open with alternating enrollment.

For Phase 2 (Cohort 2), enrollment will occur without randomization. See Section 3.1.7.2 for additional details regarding the expansion of Cohort 2.

Enrollment will be under ongoing review by an internal data safety monitoring panel (see Section 3.1.14).

### 3.1.3 Blinding/Unblinding

This is an open-label study.

### 3.1.4 Subject Population

Subjects with advanced, biopsy-accessible (as defined in Section 5.1), measurable cancers are eligible for this study, as detailed further in Section 5.

### 3.1.5 Number of Sites/Subjects

This study will be conducted at up to 8 sites in the US, with up to 102 subjects estimated for enrollment.

Phase 1 will enroll up to 36 subjects to determine the RCDs of durvalumab or durvalumab and tremelimumab within each cohort (3-6 subjects per dose level for each of the 3 cohorts). The RCD for each arm is defined as the highest dose level at which no more than 1 of 6 subjects (i.e., < 33%) experience DLTs.

Phase 2 will evaluate up to 66 subjects treated with the RCDs of the dosing regimen.

### 3.1.6 Sample Size and Statistical Considerations

**Phase 1**: The primary endpoint for the Phase 1 portion of the study is safety. The objective for Phase 1 is to determine the recommended combination dose (RCD). In each of the Phase 1 cohorts, a 3+3 design is used. Each cohort will be evaluated on its own. The only modification to the design is that the protocol evaluates up to 2 dose levels and starts at the desired dose level (Level 0). As only one drug is being modified in each cohort, the principles of a 3+3 design are applicable. The RCD for each cohort is defined as the highest dose level at which no more than 1 of 6 subjects experience DLTs.

The Cohort 1A doublet (durvalumab + polyICLC) will be enrolled first, starting at Level 0. Dose Level -1 will only be evaluated if Level 0 exceeds the RCD. Once safety is demonstrated for the subjects in the Cohort 1A doublet, the Cohort 1B triplet (durvalumab + polyICLC + IV tremelimumab) and the Cohort 1C triplet (durvalumab + polyICLC + intratumoral tremelimumab) will open to enrollment.

Based on the DLT assessment, the starting dose Level 0 will either be expanded to 6 subjects or the dose level will be reduced to Level -1. This is in accordance with a standard 3+3 design, whereby a dose level may be reduced as well as escalated based on the DLTs observed.

The table below gives the probabilities of de-escalation to dose Level -1, based on true DLT rate in the 3+3 design.

| True DLT rate | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 10% | 20% | 30% | 40% | 50% | 60% | 70% |
| Probability of de-escalation | 0.09 | 0.29 | 0.51 | 0.69 | 0.83 | 0.92 | 0.97 |

Adverse events will be summarized by maximum toxicity grade for each dose level cohort. Phase 1 will enroll up to 36 subjects to determine the RCD. Once the RCD of the triplet dosing regimen has been determined in Cohort 1C, up to 66 subsequent subjects will be enrolled into the Phase 2 cohort at the RCD according to Cohort 1C. If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2.

For the Cohort 1A doublet, if dose Level -1 is too toxic, the RCD cannot be determined and the study will stop. Otherwise, Cohorts 1B and 1C triplets will open in parallel at the doublet RCD of Cohort 1A, and the triplet RCD will be determined in both Cohorts 1B and 1C.

If no triplet RCD can be determined, Phase 2 of the study will be done at the Cohort 1A doublet RCD. If triplet RCDs are determined for both Cohorts 1B and 1C, the triplet RCD of Cohort 1C will be used in Phase 2. If a triplet RCD can only be determined in Cohort 1B, that triplet RCD will be used in Phase 2.

**Phase 2**: The phase 2 portion of the study is intended to indicate proof of concept regarding the activity of the combination selected in Phase 1, in a study of 8 disease types. The goal is to determine if there is any evidence to support future larger clinical trials of specific tumor targets. Enrollment of 6 subjects per tumor type will be allowed initially, with enrollment of an additional 6 subjects being contingent on at least one response among the initial 6 subjects. Response is defined in this protocol as achieving a partial response (PR) or complete response (CR) by immune-related RECIST or RECIST 1.1, or stable disease (SD) for at least 6 months. PD-1 receptors and PD-1 ligand have been previously investigated in Phase 1 and 2 studies. Response rates range from 8% to 25% overall, and from 10% to 35% in the squamous subpopulation (44). This combination therapy trial seeks to improve on these response rates. The stopping rule for lack of sufficient efficacy in the initial 6 subjects for each tumor type, results in a rejection rate of <20% if the true response rate for a particular tumor type is 25%. A total of (8)(6)= 48 subjects will be initially enrolled for the Phase 2 portion plus a potential additional (3)(6)= 18 subjects for three tumor types having at least one response in the initial group (total of 48+18= 66 subjects). For tumor types accruing 6+6= 12 subjects, an exact 90% confidence interval for response rate will be computed.

The safety of the regimen taken into Phase 2 will be evaluated by the Medical Monitor on an ongoing basis. When 6 subjects have been enrolled and treated in a disease cohort, a review of the data from the cohort will be conducted by the internal data safety monitoring panel and a decision (based on efficacy as well as safety) will be made whether to expand the disease cohort to 12 subjects. At any time during the study, the Medical Monitor and/or the internal data safety monitoring panel may stop the cohort or the study if the toxicity seen is not acceptable. Respective study stopping rules are described in Section 3.1.14 of the protocol.

If more than one subject in the initial group of 6 subjects in a disease type have a DLT, then accrual to that disease type cohort will be terminated.

The expansion phase sample size of 66 subjects is deemed to be sufficient for the assessment of safety and tolerability as it provides sufficient precision for estimation of adverse events. The confidence intervals (CI) for estimating the incidence of AEs ranging from 10% to 90% (in increments of 10%) are listed below. The margins of error (half width of the CI) are deemed acceptable for the estimation of AE incidences in this early phase trial.

| Number of Subjects with Event | Incidence | 95% Confidence Interval (Normal approximation) | Margin of error (half width of the CI) |
|---|---|---|---|
| 7/66 | 0.1 | (0.028, 0.172) | 0.072 |
| 14/66 | 0.2 | (0.103, 0.297) | 0.097 |
| 20/66 | 0.3 | (0.189, 0.411) | 0.111 |
| 27/66 | 0.4 | (0.282, 0.518) | 0.118 |
| 33/66 | 0.5 | (0.379, 0.621) | 0.121 |
| 40/66 | 0.6 | (0.482, 0.718) | 0.118 |
| 47/66 | 0.7 | (0.589, 0.811) | 0.111 |
| 53/66 | 0.8 | (0.703, 0.897) | 0.097 |
| 60/66 | 0.9 | (0.828, 0.972) | 0.072 |

### 3.1.7 Treatment Arms and Treatment Schema

Table 1 presents the schedule of treatment administration within each 28-day cycle. Section 3.1.7.1 (Phase 1), Table 2 and Section 3.1.7.2 (Phase 2) describe further details regarding study drug administration within each phase. See Section 6 for the sequence of drug administration on dosing days when multiple drugs are given.

NOTE: For each subject, there will be one allowed delay of up to one week for a scheduled visit; however, the delay can only occur after Cycle 1 is complete. Starting with Cycle 5, the intervals for visit days will change to ±7 days; however, a 3-week interval must be maintained between durvalumab doses (See Flowchart in Section 3.2).

- **Intratumoral administration**

  The intratumoral dose of tremelimumab was based on approximately 10% of the systemic dose, utilizing a fixed dose of 10 mg (with a de-escalation dose of 3 mg) for this study, given for 4 cycles. The intratumoral tremelimumab and intratumoral polyICLC will be administered according to the schema in Table 1 and Table 2 (see Section 6.1.3.1 for volume of tremelimumab dose).

  A 7-day dosing window is permitted for polyICLC dosing provided that all intratumoral injections are administered within the first 21 days of Cycle 1, with each injection administered at least 24 hours apart. One delay of dosing exceeding specified dosing windows may also be permitted for reasons other than toxicity (e.g., scheduling conflict, severe weather affecting travel).

  The total volume of study drug to be injected intratumorally should be administered to a single tumor if possible, but may be delivered to a maximum of 3 smaller tumors if necessary. Tumor(s) selected for injection must be identified at Baseline (pre-injection), including the volume of study drug to be administered, and the selected tumor(s) must be treated with this assigned volume for the duration of the study.

- **Systemic administration** will be delivered in accordance with the dose de-escalation schema (see Table 2) to determine the RCDs. The treatment schema in Table 1 will be followed for all cohorts. Following completion of intratumoral dosing in Cycle 1 and throughout Cycle 2, polyICLC will be administered at a dose of 1 mg IM twice weekly. During Cycle 3, polyICLC will be administered on Days 1 and 4 and will be discontinued thereafter.

**Table 1. Treatment Schema**

| COHORT N | 28 DAY CYCLE | CHECKPOINT ANTIBODIES[a] | | TME MODULATOR |
|---|---|---|---|---|
| | | Tremelimumab | Durvalumab | PolyICLC |
| Cohort 1A n = 3 to 6 per dose level | 1 | | IV Day 1 | 1 mg ITM (Days 1, 3, 5, 8, 10 and 15)[b] 1 mg IM Days 17, 22, and 24 |
| | 2 | | IV Day 1 | 1 mg IM Days 1, 3, 8, 10, 15, 17, 22, 24 |
| | 3 | | IV Day 1 | 1 mg IM Days 1 and 4 of cycle, then stop |
| | 4-12 | | IV Day 1 | – |
| Cohort 1B n = 3 to 6 per dose level | 1 | IV Day1 | IV Day 1 | 1 mg ITM (Days 1, 3, 5, 8, 10 and 15)[b] 1 mg IM Days 17, 22, and 24 |
| | 2 | IV Day1 | IV Day 1 | 1 mg IM Days 1, 3, 8, 10, 15, 17, 22, 24 |
| | 3 | IV Day1 | IV Day 1 | 1 mg IM Days 1 and 4 of cycle, then stop |
| | 4 | IV Day1 | IV Day 1 | |
| | 5-12 | – | IV Day 1 | – |
| Cohort 1C n = 3 to 6 per dose level | 1 | ITM Days 1, 8, and 15 | IV Day 1 | 1 mg ITM (Days 1, 3, 5, 8, 10 and 15)[b] 1 mg IM Days 17, 22, and 24 |
| | 2 | ITM Days 1 and 15 | IV Day 1 | 1 mg IM Days 1, 3, 8, 10, 15, 17, 22, 24 |
| | 3 | ITM Day 1 | IV Day 1 | 1 mg IM Days 1 and 4 of cycle, then stop |
| | 4 | ITM Day 1 | IV Day 1 | |
| | 5-12 | | IV Day 1 | – |
| Cohort 2 n = up to 66 | 1 | RCD ITM Days 1, 8 and 15 | IV Day 1 | 1 mg ITM (Days 1,3, 5, 8, 10 and 15)[b] 1 mg IM Days 17, 22, and 24 |
| | 2 | RCD ITM Days 1 and 15 | IV Day 1 | 1 mg IM Days 1, 3, 8, 10, 15, 17, 22, 24 |
| | 3 | RCD ITM Day 1 | IV Day 1 | 1 mg IM Days 1 and 4 of cycle, then stop |
| | 4 | RCD ITM Day 1 | IV Day 1 | |
| | 5-12 | | IV Day 1 | – |

RCD = recommended combination dose; TME = tumor microenvironment; IM = intramuscularly; ITM = intratumorally; IV = intravenously

[a] Total doses to be administered are outlined in Table 2.

[b] A 7-day dosing window is permitted provided that all injections are administered within the first 21 days of Cycle 1; injections must be administered ≥ 24 hours apart.

Note: If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2.

#### 3.1.7.1 Phase 1: Dose-finding Cohorts

During Phase 1, subjects will be evaluated for DLTs as defined in Section 3.1.9. There will be enrollment to 3 subject cohorts, with staggered initiation of enrollment. The dose levels to be evaluated in Phase 1 are presented in Table 2, according to the treatment schema in Table 1. Dose de-escalations for the determination of the RCDs will be performed based on the respective rules for a standard 3 + 3 study design, as displayed in Figure 1.

Within each cohort, the first study drug administration for the first subject and the second subject will be separated by at least 14 days.

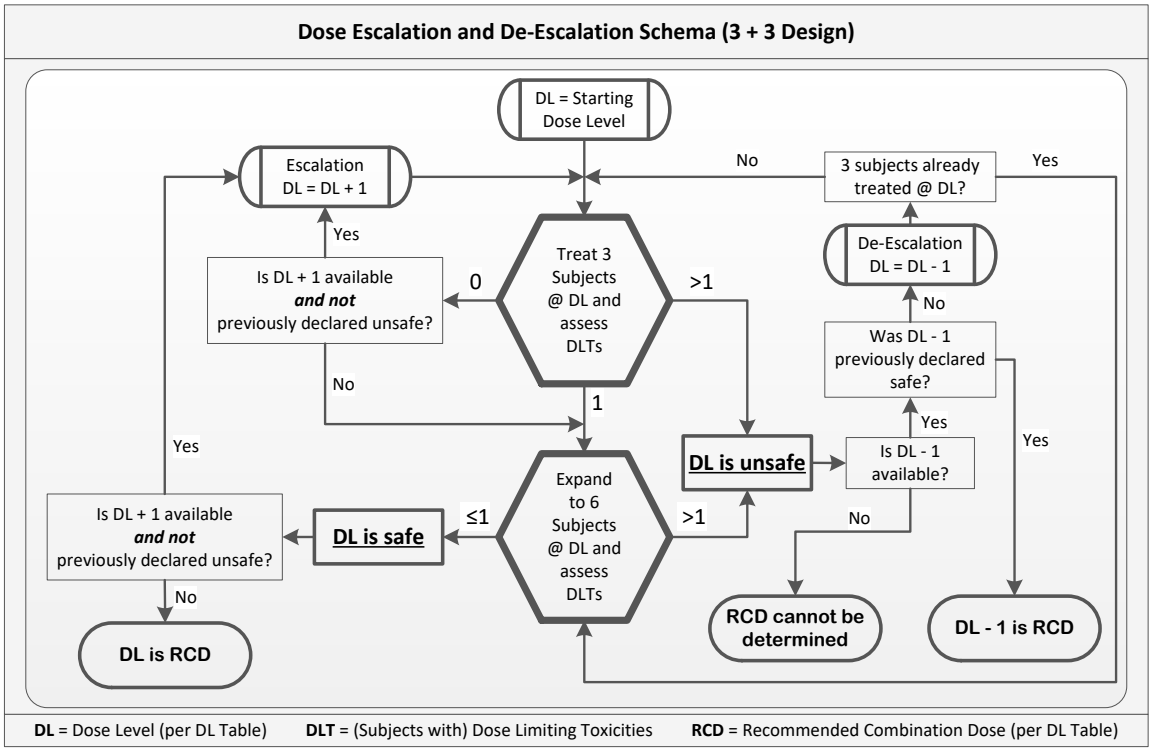
**Table 2. Phase 1 Dose Levels**

| **Cohort 1A** | | | |
|---|---|---|---|
| **Dose Level** | **Durvalumab Q4W (IV)** | **PolyICLC (ITM/IM)** | |
| -1 | 750 mg | 1 mg | |
| ***0 (Starting Level)*** | ***1500 mg*** | ***1 mg*** | |
| **Cohort 1B** | | | |
| **Dose Level** | **Durvalumab Q4W (IV)** | **PolyICLC (ITM/IM)** | **Tremelimumab Q4W (IV)** |
| -1 | RCD from Cohort 1A | 1 mg | 22.5 mg |
| ***0 (Starting Level)*** | ***RCD from Cohort 1A*** | ***1 mg*** | ***75 mg*** |
| **Cohort 1C** | | | |
| **Dose Level** | **Durvalumab Q4W (IV)** | **PolyICLC (ITM/IM)** | **Tremelimumab (ITM)** |
| -1 | RCD from Cohort 1A | 1 mg | 3 mg |
| ***0 (Starting Level)*** | ***RCD*** from Cohort 1A | ***1 mg*** | ***10 mg*** |

Q4W = every 4 weeks; IV = intravenous; ITM = intratumoral; IM = intramuscular

**NOTE: The durvalumab dose of 1500 mg Q4W is for subjects > 30 kg.** If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

**Figure 1: Dose Escalation and De-escalation Schema**




As per the schema above, the RCD for each cohort is defined as the highest dose level at which no more than 1 of 6 subjects (i.e., < 33%) experience DLTs. The RCD cannot be determined if none of the predefined dose levels fulfill that criterion.

### 3.1.7.2 Phase 2: Expansion Phase

Once the RCD of the triplet dosing regimen has been determined in Cohort 1C, subsequent subjects will be enrolled into Cohort 2 to receive the RCDs of both checkpoint antibodies in combination with polyICLC, according to the treatment schema in Table 1. Up to 66 evaluable subjects will be treated in Cohort 2. If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2.

Cohort 2 will expand the cohort that was treated at the RCD from the dose-finding phase. Up to 6 subjects per tumor type will be initially enrolled into Cohort 2. Data from all subjects who are treated with the dosing regimen in either the cleared dose-finding cohort or Cohort 2 will be reviewed for safety/efficacy to select up to 3 tumor types that demonstrate an efficacy signal, defined as at least 1 of 6 subjects within a tumor type who achieve a partial response (PR) or complete response (CR) by immune-related RECIST (irRECIST) or RECIST 1.1, or stable disease (SD) for at least 6 months (See Section 3.1.6 regarding DLT assessment during expansion). Up to 6 additional subjects with each of the selected tumor types may be enrolled as an expansion of Cohort 2. If more than 3 of the tumor types have a signal, selection of 2-3 with the greatest signal may be selected for continuation.

NOTE: Cutaneous T cell lymphomas (CTCL) may respond very differently than solid tumors; therefore, the study will primarily focus on solid tumors, but a “signal-seeking” approach to

including some subjects with CTCL will be supported. There will be a limit of < 10-20% CTCL for total enrollment.

See Section 4.3.1.1 for details on tumor biopsies.

### 3.1.8 Dosing Adjustments, Delays, and Discontinuations

Dose adjustment and management guidelines for toxicity related to tremelimumab and durvalumab and for polyICLC are outlined in Section 8.3 and Section 8.4, respectively.

If subject(s) experience excessive toxicity related clearly and exclusively to a single checkpoint antibody or polyICLC, that agent will be discontinued, but the subject(s) may continue to receive the other study drug(s) within their assigned regimen, provided that no additional safety concerns are observed.

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline (i.e., the guideline that provides for the greatest dose reduction, dose delays or holds) should be followed.

### 3.1.9 Dose-limiting Toxicity

DLTs will be assessed for the period from Day 1 of the study up to and including the Week 7, Cycle 2/Day 15 study visit; this is defined as the "DLT Evaluation Period" for each subject in Cohorts 1A through 1C. The decisions for dose de-escalations and RCD, as described in Section 3.1.7.1, will be based primarily on the number of subjects with DLTs occurring during the DLT Evaluation Period. DLTs occurring outside the DLT Evaluation Period will also be evaluated and may impact such decisions.

DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of tremelimumab, durvalumab, and/or polyICLC and fulfill any of the following criteria:

1. Any Grade ≥ 3 colitis, pneumonitis, neurological event, or uveitis.
2. Any Grade 2 pneumonitis, neurological event, or uveitis with the *following exception*:
   - Grade 2 pneumonitis, neurological event, or uveitis that downgrades to Grade ≤ 1 within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
3. Any *other* Grade ≥ 3 toxicity, with the *following exceptions*:
   - Grade 3 irAEs (see definition below) that downgrade to Grade ≤ 2 within 3 days, or to Grade ≤ 1 or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Grade 3 endocrinopathy that becomes asymptomatic when managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
   - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
   - Grade 3 fatigue for ≤ 7days.
   - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.

- Liver transaminase elevation ≤ 8 times ULN that downgrades to Grade ≤ 2 (≤ 5 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Total bilirubin ≤ 5 times ULN that downgrades to Grade ≤ 2 (≤ 3 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Grade ≥ 3 neutropenia that (1) is not associated with fever or systemic infection, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Grade 3 or Grade 4 lymphopenia.
- Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Grade 3 or 4 asymptomatic increases in amylase or lipase levels for which appropriate evaluation shows no clinical evidence of pancreatitis.

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

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or is listed as exempt above may also be defined as DLT after consultation with the Sponsor and Investigators, based on the emerging safety profiles of tremelimumab, durvalumab, and polyICLC. Likewise, subjects who become not evaluable for DLT because they discontinued or interrupted treatment due to toxicities other than DLTs may be counted as DLT subjects, if the toxicities cannot be managed in accordance with the dosing modifications described in Section 3.1.8.

Subjects who experience a DLT will be discontinued from study therapy and will enter the On Study and Post Study Follow-up phases of the study (see Section 3.1.16). However, if it is in the best interest of the subject, the Investigator and Sponsor may agree to continue treatment, possibly at a lower dose level.

Maximum tolerated doses (MTDs) will not be determined. Instead, RCDs will be determined in the context of the predefined dose levels used during the dose de-escalation phase as per Section 3.1.7.1.

### 3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Withdrawal of consent for further treatment
2. Pregnancy or intent to become pregnant.
3. DLT (see Section 3.1.9, including exception).
4. Progressive disease by irRECIST requiring alternative systemic treatment (see NOTE below).
5. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
6. Development of intercurrent, non-cancer-related illnesses or complications that prevent either continuation of therapy or regular follow-up.
7. Best medical interest of the subject (at the discretion of the Investigator)

A subject will be **withdrawn from the study** for the following reasons:

1. Best medical interest of the subject at the discretion of the Investigator.
2. Initiation of alternative anticancer therapy (marketed or investigational).
3. Withdrawal of consent for all follow-up.
4. Lost to follow-up.
5. Death.

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. If applicable, subjects who are withdrawn from study treatment should undergo the planned On Study Follow-up procedures (see Section 3.2) and enter the Post Study follow-up period (see Section 3.1.16).

NOTE: Subjects meeting criteria for radiographic progression by irRECIST (Section 8.5) will be allowed to continue on therapy until confirmation of progression by irRECIST if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
b. No significant decline in ECOG performance status;
c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Section 7.2.6 provides additional details regarding documentation for early subject withdrawal from study treatment and early withdrawal from study.

See also Sections 8.3 and 8.4 for subject withdrawal from treatment due to necessary dosing interruptions or discontinuations.

### 3.1.11 Evaluability and Subject Replacement

Phase 1: Subjects in Cohorts 1A through 1C are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment. The **Per-Protocol (PP) Population for DLT Assessment** includes:

(1) All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9.
(2) All subjects with no DLT who receive at least 75% of the total dose of each study drug and undergo respective safety assessments, without major protocol violations, over the entire DLT evaluation period.

Subjects who are not fully evaluable for DLT will be replaced.

Phase 2: Subjects in Cohort 2 are considered fully evaluable and will be included in the **Per-Protocol (PP) Analysis Population for Clinical Efficacy** if they meet the following criteria:

- Receive at least the following minimum quantities of study drugs over the subject's entire treatment period:
  - 2 durvalumab administrations
  - 3 tremelimumab administrations
  - 10 polyICLC administrations (regardless of route)
- Undergo appropriate disease assessments (radiological or clinical)
- Have no major protocol violations that would have an effect on the efficacy evaluation.

Subjects who are not fully evaluable for PP population for Clinical Efficacy may be replaced.

### 3.1.12 Optional Study Treatment Extension

Treatment extension beyond 12 cycles is not planned.

### 3.1.13 Interim Analysis

Safety analyses will be performed to assess DLTs in Cohorts 1A through 1C (see Section 3.1.9). Analyses of the initial 6 subjects treated with each tumor type in Cohort 2 will be assessed to determine whether to enroll 6 more subjects (see Section 3.1.6).

### 3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements section of the protocol (see Section 7), Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and co-investigators as needed), the Sponsor's Medical Monitor, and drug safety personnel from Medimmune and Oncovir, providers of the study drugs. Additional investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews as indicated. An Independent Data Monitoring Board will not be utilized for this open-label study.

The study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to 1 or more of the study drugs.
2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to 1 or more of the study drugs.
3. Any events that, in the judgment of the medical monitor, are deemed serious enough to warrant immediate review by the data safety monitoring panel. This may include any symptomatic and/or irreversible treatment-related Grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related Grade ≥ 3 neurological toxicity or uveitis.
4. Any other safety finding assessed as related to 1 or more study drugs that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

### 3.1.15 Duration of Treatment and Study

#### 3.1.15.1 Duration of Treatment

Subjects may receive study treatment until 1 of the criteria for withdrawal is met (see Section 3.1.10) or until the maximum duration for each study drug is met, defined as 12 cycles of durvalumab, 4 cycles of tremelimumab, and 3 cycles of polyICLC.

#### 3.1.15.2 Duration of Study

| | |
|---|---|
| Duration of Study per Subject: | Up to 12 months treatment + 3 months On Study Follow-up |
| Enrollment Period: | 24 months |
| Length of Study: | 39 months (not including Post Study Follow-up as described in Section 3.1.16)<br>NOTE: Per Amendment 6.0, all post study follow-up for the collection of survival data will be discontinued as of 28 February 2022 (see rationale in Section 8.1, Amendment 6.0 on Page 80). |

### 3.1.16 On Study and Post Study Follow-up

All subjects, whether they complete the study as planned, discontinue treatment, or prematurely withdraw from the study as per Section 3.1.10, will be followed as per institutional guidelines in accordance with the usual standard of care principles.

For subjects who complete the study or who discontinue treatment prematurely, On Study Follow-up will be conducted for 90 days after the last study drug administration according to the flowchart in Section 3.2. Refer to Section 7.1.5 for information on recording AEs during the On Study Follow-up.

If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On-Study Follow-up Period (which is 28 days after the last dose of study treatment), any assessments required in the 28 day post-last treatment visit that are not covered as part of the last on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the last on-treatment visit and the 28 day post-last treatment visit should not be repeated.

In addition to the On Study Follow-up, there will be a Post Study Follow-up, during which clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 3 months for 2 years after completion of treatment, then every 6 months until 5 years from study entry, then annually until 10 years from study entry.

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug.

NOTE: Per Amendment 6.0, all post study follow-up for the collection of survival data will be discontinued as of 28 February 2022 (see rationale in Section 8.1, Amendment 6.0 on Page 80).

For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal

Investigator, will obtain the data through review of outside records or communication with the subject or his/her physician.

## 3.2 Study Flowchart

| LUD 2014-011 Study Flowchart | Screening / Baseline (Day -21 to -1) | Treatment | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 (4 weeks) | | | | | | | | | Cycle 2 (4 weeks) | | | | | | | | Cycle 3 (4 weeks) | | Cycle 4 (4 weeks) | Cycle 5 (4 weeks) |
| **Study Week** | | 1 | | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 13 | 17 |
| **Cycle Day[1,2]** | | 1±3 | 3±3 | 5±3 | 8±3 | 10±3 | 15±3 | 17±3 | 22±3 | 24±3 | 1±3 | 3±3 | 8±3 | 10±3 | 15±3 | 17±3 | 22±3 | 24±3 | 1±3 | 4±3 | 1±3 | 1±7 |
| **Study Day** | | 1 | 3 | 5 | 8 | 10 | 15 | 17 | 22 | 24 | 29 | 31 | 36 | 38 | 43 | 45 | 50 | 52 | 57 | 60 | 85 | 113 |
| **Study Drug Administration** | | | | | | | | | | | | | | | | | | | | | | |
| Durvalumab IV (all cohorts) | | X | | | | | | | | | X | | | | | | | | X | | X | X |
| Tremelimumab IV (Cohort 1B only) | | X | | | | | | | | | X | | | | | | | | X | | X | |
| Tremelimumab, intratumoral (Cohort 1C and Cohort 2 if 1C is cleared in Phase 1) | | X | | | X | | X | | | | X | | | | X | | | | X | | X | |
| Poly ICLC, Intratumoral[4] | | X | X | X | X | X | X | | | | | | | | | | | | | | | |
| Poly ICLC IM | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| **Tumor and Disease Assessments** | | | | | | | | | | | | | | | | | | | | | | |
| Disease Staging (date/stage at 1st diagnosis and at study entry) | X | | | | | | | | | | | | | | | | | | | | | |
| Disease Assessment by irRECIST/RECIST1.1 (and imaging)[8] | X | | | | | | | | | | | | | | | | | | | | X | |
| **Study Procedures and Examinations** | | | | | | | | | | | | | | | | | | | | | | |
| Eligibility Assessment and Informed Consent (IC)[9] | X | | | | | | | | | | | | | | | | | | | | | |
| Demographics (DoB, sex, height, race, ethnicity) | X | | | | | | | | | | | | | | | | | | | | | |
| Physical Examination (incl. weight and ECOG PS) | X | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | |
| Vital Signs (T, HR, BP, RR)[10] | X | X | X | X | X | X | X | X | | | X | | | | X | | | | X | | X | X |
| 12- Lead ECG | X | | | | | | | | | | | | | | | | | | | | | |
| Concomitant Medication (name, indication, dose, route, start & end dates) /Procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events (starting/worsening after IC)[6] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Specimens for Routine Laboratory Procedures** | | | | | | | | | | | | | | | | | | | | | | |
| Blood Hematology (CBC, differential, platelets)[3] | Day -7 to -1 | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| Chemistry (Glucose, BUN, creat, Na, K, Cl, CO2, Ca, Mg, protein, alb, Tbili, AST, ALT, ALP, LDH)[3] | Day -7 to -1 | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| Chemistry cont: Free T3, Free T4, TSH[3] | Day -7 to -1 | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| Chemistry cont: Amylase and lipase[3] | Day -7 to -1 | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| Hemoglobin A1c | Day -7 to -1 | | | | | | | | | | | | | | | | | | | | | |
| Serum Pregnancy Test (urine only Day 1)[3] | Day -7 to -1 | X | | | | | | | | | X | | | | | | | | X | | | X |
| Coagulation (PT, aPTT, INR)[3] | Day -7 to -1 | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| Urinalysis[3] | Day -7 to -1 | X | | | X | | X | | | | X | | | | X | | | | X | | X | X |
| **Blood for Biological Markers** | | | | | | | | | | | | | | | | | | | | | | |
| Circulating soluble factors (Antibody, Chemokines, Cytokines -serum) | X | X[3] | | | X[3] | | X[3] | | | | X[3] | | | | | | | | X[3] | | X[3] | |
| PBMCs (Flow cytometry, T-cell Responses and Circulating T-cells) | X | X[3] | | | X[3] | | X[3] | | | | X[3] | | | | | | | | X[3] | | X[3] | |
| RNA profiling (whole blood) | X | | | | X[3] | | X[3] | | | | X[3] | | | | | | | | X[3] | | X[3] | |
| **Other Procedures** | | | | | | | | | | | | | | | | | | | | | | |
| Tumor Biopsy[5] | X | | | | | | X[3] | | | | X[3] | | | | | | | | | | | |
| **Long-Term Follow-up[12]** | | | | | | | | | | | | | | | | | | | | | | |
| Overall Survival | | | | | | | | | | | | | | | | | | | | | | |
| Progression-free Survival[7] | | | | | | | | | | | | | | | | | | | | | | |

| LUD 2014-011 Study Flowchart (cont.) | Treatment | | | | | | | Visit for Subjects who Discontinue Treatment Prematurely | On Study Follow-up | | | Post Study Follow-up[12] Every 3 mos for 2 yrs after completion of treatment; then every 6 mos until 5 yrs from study entry; then yearly until 10 yrs from study entry |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 6 (4 weeks) | Cycle 7 (4 weeks) | Cycle 8 (4 weeks) | Cycle 9 (4 weeks) | Cycle 10 (4 weeks) | Cycle 11 (4 weeks) | Cycle 12 (4 weeks) | | Last Study Drug +28±3 days | Last Study Drug +56±3 days | Last Study Drug +91±7 days | |
| **Study Week** | 21 | 25 | 29 | 33 | 37 | 41 | 45 | | | | | |
| **Cycle Day[1,2]** | 1±7 | 1±7 | 1±7 | 1±7 | 1±7 | 1±7 | 1±7 | | | | | |
| **Study Day** | 141 | 169 | 197 | 225 | 253 | 281 | 309 | | | | | |
| **Study Drug Administration** | | | | | | | | | | | | |
| Durvalumab IV (all cohorts) | X | X | X | X | X | X | X | | | | | |
| Tremelimumab IV (Cohort 1B only) | | | | | | | | | | | | |
| Tremelimumab, intratumoral (Cohort 1C and Cohort 2 if 1C is cleared in Phase 1) | | | | | | | | | | | | |
| Poly ICLC, Intratumoral[4] | | | | | | | | | | | | |
| Poly ICLC IM | | | | | | | | | | | | |
| **Tumor and Disease Assessments** | | | | | | | | | | | | |
| Disease Staging (date/stage at 1st diagnosis and at study entry) | | | | | | | | | | | | |
| Disease Assessment by irRECIST/RECIST1.1 (and imaging)[8] | | X | | X | | X | | X | X | | | |
| **Study Procedures and Examinations** | | | | | | | | | | | | |
| Eligibility Assessment and Informed Consent (IC)[9] | | | | | | | | | | | | |
| Demographics (DoB, sex, height, race, ethnicity) | | | | | | | | | | | | |
| Physical Examination (incl. weight and ECOG PS) | X | X | X | X | X | X | X | X | X | X | X | |
| Medical History | | | | | | | | | | | | |
| Vital Signs (T, HR, BP, RR)[10] | X | X | X | X | X | X | X | X | X | X | X | |
| 12- Lead ECG | | | | | | | | | | | | |
| Concomitant Medication (name, indication, dose, route, start & end dates) /Procedures | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse Events (starting/worsening after IC)[6] | X | X | X | X | X | X | X | X | X | X | X | |
| **Specimens for Routine Laboratory Procedures** | | | | | | | | | | | | |
| Blood Hematology (CBC, differential, platelets)[3] | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry (Glucose, BUN, creat, Na, K, Cl, CO2, Ca, Mg, protein, alb, Tbili, AST, ALT, ALP, LDH)[3] | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry cont: Free T3, Free T4, TSH[3] | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry cont: Amylase and lipase[3] | X | X | X | X | X | X | X | X | X | X | X | |
| Hemoglobin A1c | | | | | | | | | | | | |
| Serum Pregnancy Test (urine only Day 1)[3] | | X | | X | | X | | X | X | | X | |
| Coagulation (PT, aPTT, INR)[3] | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis[3] | X | X | X | X | X | X | X | X | X | X | X | |
| **Blood for Biological Markers** | | | | | | | | | | | | |
| Circulating soluble factors (Antibody, Chemokines, Cytokines -serum) | | X[3] | | | | | X[3] | X | X[11] | | | |
| PBMCs (Flow cytometry, T-cell Responses and Circulating T-cells) | | X[3] | | | | | X[3] | X | X[11] | | | |
| RNA profiling (whole blood) | | X[3] | | | | | X[3] | X | X[11] | | | |
| **Other Procedures** | | | | | | | | | | | | |
| Tumor Biopsy[5] | | | | | | | | optional | optional | | | |
| **Long-Term Follow-up[12]** | | | | | | | | | | | | |
| Overall Survival | | | | | | | | | | | | X[12] |
| Progression-free Survival[7] | | | | | | | | | | | | X[12] |

**Study Flowchart Footnotes**

| |
|---|
| 1. For each subject, there will be one allowed delay of up to one week for a scheduled visit; however, the delay can only occur after Cycle 1 is complete |
| 2. Starting with Cycle 5, the intervals for visit days will change to ±7 days; however, a 3-week interval must maintained between durvalumab doses. |
| 3. Collected pre-dose (prior to drug administration). It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing. |
| 4. For intratumoral polyICLC, a 7-day dosing window is permitted provided that all injections are administered within the first 21 days of Cycle 1; injections must be administered ≥ 24 hours apart |
| 5. Also conducted at time of progression and end of treatment; injected and uninjected tumors on Day 15 and Cycle 2 Day 1, and from the same lesion each time if possible. See Sections 4.3.1.1 and 5.1 (#2) for details on biopsies.<br>Note: the Screening/Baseline biopsy may be done on the Cycle 1/Day 1 Visit as long as it is done prior to start of any treatment. |
| 6. See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration. |
| 7. For subjects who did not experience progression while on study |
| 8. Subsequent imaging at 4 to 8 weeks after first documentation of irRECIST-defined progression must be performed. |
| 9. Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart |
| 10. See Section 6.5 for assessment before/during/after IV infusions; Section 6.1.3.1 for intratumoral tremelimumab vitals assessments; Section 6.3.3 for intratumoral and IM polyICLC vitals assessments. |
| 11. There is no need to repeat these assessments if they were done at the Premature Discontinuation Visit or at the last on treatment visit. |
| 12. Per Amendment 6.0, all post study follow-up for the collection of survival data will be discontinued as of 28Feb2022 (see Section 8.1, Amendment 6.0) |

# 4 Study Objectives and Endpoints

| | |
|---|---|
| **Primary Objective [Endpoints]** | **Dose-finding Phase (Cohorts 1A – 1C):**<br>*Safety and Tolerability* [DLTs, RCDs According to CTCAE V4.03]<br>**Expansion Phase (Cohort 2):**<br>*Clinical Efficacy by irRECIST and RECIST 1.1* [ORR, PFS, OS] |
| **Secondary Objectives [Endpoints]** | **All Subjects:**<br>*Safety and Tolerability* [According to CTCAE V4.03]<br>*Clinical Efficacy by irRECIST and RECIST 1.1** [ORR, PFS, OS]<br>*unless assessed as Primary Objective/Endpoint |
| **Exploratory Objectives [Endpoints]** | **All Subjects:**<br>*Biologic Activity* [Effects on Tumor Microenvironment, Immune Responses] |

CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCD = recommended combination dose; RECIST = Response Evaluation Criteria in Solid Tumors

## 4.1 Safety and Tolerability

The safety and tolerability of each regimen will be evaluated to determine the tolerability of intratumoral or systemic tremelimumab and/or IV durvalumab in combination with polyICLC. Safety will be evaluated by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the investigators.

### 4.1.1 Endpoints and Assessment Methods

Laboratory tests, vital sign measurements, physical examinations, and subject interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as AEs. All treatment-emergent, clinically significant abnormalities and deteriorations from the time of informed consent to the End of Study Visit should be recorded in the Case Report Forms as AEs and graded according to the NCI CTCAE, Version 4.03.

### 4.1.2 Subject Evaluation and Statistics

See Section 3.1.11 for subject evaluability and replacement for DLT assessments and for description of the **Per-Protocol (PP) Population for DLT Assessment**.

In addition, all subjects who receive at least 1 dose of tremelimumab, durvalumab, or polyICLC will be assessed for safety and tolerability, regardless of whether or not they are fully evaluable per protocol as defined in Section 3.1.11; this is the **Safety Population.** Appropriate summaries of AEs, SAEs, DLTs, laboratory data, and vital sign data will be presented. AEs will be listed individually per subject according to the NCI CTCAE, Version 4.03, and the number of subjects experiencing each AE will be summarized using descriptive statistics.

Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after

dosing) will be presented overall and by maximum severity (according to CTCAE version 4.03) and relationship to study medication.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

## 4.2 Clinical Efficacy

### 4.2.1 Endpoints and Assessment Methods

Clinical efficacy will be determined by objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Disease assessments will be done in accordance with the flowchart in Section 3.2. Subsequent imaging at 4 to 8 weeks after first documentation of irRECIST-defined progression must be performed.

#### 4.2.1.1 Objective Response Rate

The primary method of assessment of response and ORR will be irRECIST (see Section 8.5) and the secondary method will be RECIST 1.1, modified for the tumor biopsies such that tumors biopsied during the study will not be considered measurable for ORR but will be assessed as non-measurable lesions to the extent that marked progression of a non-measurable lesion is inconsistent with an objective response; these lesions will be identified prospectively prior to the first treatment. ORR is defined as the percentage of evaluable subjects meeting criteria of CR or PR, confirmed at a subsequent time point (≥ 4 weeks). Disease control is defined as SD for 6 months, PR, or CR. Every attempt should be made to use whichever imaging technique(s) and test(s) are used initially for repeat evaluations throughout the study, whereby the End of Study tumor assessments will be at least 4 weeks from the prior assessment. Regression of treated and untreated tumors will be recorded separately and tracked as well.

#### 4.2.1.2 Progression-free Survival

Progression-free survival will be defined as the number of days from the date of first dose of study drug to the date of earliest disease progression based on irRECIST, or to the date of death, if disease progression does not occur. PFS based on RECIST 1.1 will also be recorded but will not be the primary endpoint.

#### 4.2.1.3 Overall Survival

OS will be measured for each subject from the date of first dose of study drug until the recorded date of death or last follow-up. Subjects who are still alive will be censored on the date of last follow-up. Every effort will be made to follow subjects for OS after they discontinue the study.

NOTE: Per Amendment 6.0, all post study follow-up for the collection of survival data will be discontinued as of 28 February 2022 (see rationale in Section 8.1, Amendment 6.0 on Page 80).

### 4.2.2 Subject Evaluation and Statistics

The analysis of clinical efficacy will be based on both the intent-to-treat (ITT) and the PP population for Clinical Efficacy. Subjects who receive at least 1 dose of any study drug will be included in the ITT population. Subjects who are fully evaluable per protocol, as defined in Section 3.1.11, will be included in the PP population for Clinical Efficacy.

## 4.3 Biological Activity

### 4.3.1 Endpoints and Assessment Methods

Correlative data will be obtained to assess the effects of the dosing regimen on the TME, including PD-L1 expression (baseline by tumor type, changes over time during and after intratumoral therapy), T-cell infiltration, chemokine profiles, immune gene signatures, TLR signaling, and markers of immunogenic cell death (LC3, intact ER stress response, HMGB1).

Any observed effects will also be assessed to determine whether these changes (or baseline levels) may predict clinical response to combination therapy, including blockade of PD-L1 and CTLA-4.

#### 4.3.1.1 Tumor Microenvironment

Tumor biopsies will be conducted on all subjects at Baseline (pretreatment), Day 15, and, provided there is sufficient tumor to biopsy, at Day 29 (Cycle 2, Day 1), and optionally at the time of progression and at the end of treatment. Subjects must have adequate tissue available as outlined in the inclusion criteria (Section 5.1). Biopsies will be obtained via incisional, excisional, or core biopsies. Additional biopsies may be obtained as appropriate. These biopsies will be prepared in 3 conditions: formalin-fixed tissue, quick-frozen tissue, and RNAlater®. In subjects with large biopsies, viable cell suspensions may be collected and prepared as single-cell suspensions and viably cryopreserved. Endpoints include induction of a favorable immune signature and increased T-cell infiltration, as well as pre-treatment and post-treatment immune signatures that predict clinical response.

Ideally, tumor biopsies will include both injected tumor and non-injected tumor, to study abscopal effects. The tumor biopsies ideally will also come from the same lesion each time, if possible.

These specimens will be evaluated for the following endpoints, using the listed assessment methods:

| Endpoint | Approach | Specific measure | Analytic method |
|---|---|---|---|
| PD-L1 expression | IHC | PD-L1 | Automated image analysis and pathologist review |
| T cell infiltrates and immunotypes associated with improved survival (45-49) | IHC and/or IF | CD45, CD3, CD8, CD4/FoxP3, CD20, CD31, Ki67, CD45RO | Automated image analysis and pathologist review; apply Immunoscore parameters to assess changes in the TME |
| Innate immune cell infiltrates | IHC | macrophage markers (CD68, CD163), myeloid markers (CD11b, CD33), DC markers (CD11c, CD1a, DC-LAMP/CD208), CD1c and NK cell markers (CD56) | |
| Chemokine profiles, immune signatures associated with improved survival and response to immune therapy (50-54) | Affymetrix gene expression arrays, and customized nanostring panel with 100 molecules including markers of inflammation, common cancer antigens and certain biomarkers from Melbourne/J Cebon | Genes associated with Th1 responses; plus genes of immune regulation (PDL1, IDO, etc.) | Partek Genomic Suite and IPA software |
| Immunogenic cell death machinery | IHC | LC3, intact ER stress response, HMGB1 | Automated image analysis |
| TLR signaling | Gene expression arrays as specified above | MyD88, adaptor proteins, chemokines and NFkB activation | Partek Genomic Suite and IPA software |
| Functional markers | IHC, protein array, and/or flow cytometry | Arginase, iNOS, CD73, CD39, CD40 and IDO | |
| Markers of T cell activity, | Flow cytometry | OX40, GITR, CD137, IFN and granzyme, perforin. | |
| TCR and/or BCR diversity | High throughput analysis | TCRV-beta, BCR | |

IF = immunofluorescence; IHC = immunohistochemistry; IPA = Ingenuity Pathway Analysis; TME = tumor microenvironment; TLR = toll-like receptor

#### 4.3.1.2 Pharmacodynamics

Blood samples for exploratory pharmacodynamic assessments will be collected at each visit and time point as noted in Section 3.2.

Exploratory pharmacodynamic assessments may include, but are not be limited to:

- PBMCs to assess immune cell phenotypes by flow cytometry, which may include T cell phenotype and activation markers, B cells, myeloid derived suppressor cells and/or immune diversity. The PBMCs will also be used for measurement of T cell responses to defined antigens.
- Serum levels of circulating soluble factors, including antibodies, cytokines, and chemokines.
- Whole blood for mRNA/miRNA profiling.

### 4.3.2 Subject Evaluation and Statistics

Only subjects who receive at least 1 dose of durvalumab, tremelimumab and polyICLC or durvalumab and polyICLC, and provide the baseline and at least 1 post-treatment sample (if applicable) will be evaluated. Exploratory results will be summarized descriptively.

# 5 Subject Eligibility

NOTE: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

## 5.1 Inclusion Criteria

*Eligible subjects **must fulfill** all of the following criteria:*

| | |
|---|---|
| 1. | Subjects must have histologic confirmation of advanced unresectable disease, have failed at least one standard of care therapy, and do not have curative options. Tumors should be biopsy-accessible (see NOTE 1), measurable cancers of the following histologies:<br>• Non-viral-associated head and neck squamous cell carcinoma (HNSCC) or HPV-associated HNSCC after failure of prior therapy<br>• Locally recurrent or metastatic breast cancer<br>• Sarcoma<br>• Merkel Cell Carcinoma (MCC)<br>• Cutaneous T cell Lymphoma (CTCL)<br>• Melanoma after failure of available therapies<br>• GU cancers with accessible metastases (e.g., bladder, renal)<br>• Any solid tumors with masses that are accessible<br>NOTE 1: A biopsy-accessible lesion is defined as a tumor lesion which can be, in the opinion of the Investigator or that of consulting physicians, safely accessed for biopsy or for injection by means of physical examination or imaging guided means, preferably ultrasound (e.g., cutaneous lesions, inguinal nodes, supraclavicular or cervical nodes, superficial abdominal lesions, and lesions that are accessible by ultrasound guidance and not impacting vital organs/structures).<br>NOTE 2: CTCL may respond very differently than solid tumors; therefore, the study will primarily focus on solid tumors, but a "signal-seeking" approach to including some subjects with CTCL will be supported. There will be a limit of < 10-20% CTCL for total enrollment |
| 2. | Subjects need to have at least 2 lesions, as follows:<br>(1) 1 lesion considered measurable disease as defined by irRECIST and RECIST 1.1, i.e., that can be accurately measured in at least 1 dimension (longest diameter to be recorded), where each lesion must be ≥ 10 mm when measured by computed tomography (CT), magnetic resonance imaging (MRI), or caliper measurement by clinical examination, or ≥ 20 mm when measured by chest x-ray. To be considered measurable, lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI. <u>These lesions should not be injected with study drug or biopsied.</u><br>(2) 1 larger lesion (approximately 2 cm or more) amenable to repeated multiple core biopsies or at least 3 smaller lesions of at least 6 mm diameter amenable to repeated single core biopsy, measured by clinical examination. Multiple small lesions of comparable volume may be biopsied on a single date. <u>These lesions must also be</u> |

| | |
|---|---|
| | suitable for repeated injections of study drug, either as single injection in larger lesions (preferred) or multiple injections in up to 3 smaller lesions.<br>Ideally, subjects should have at least 1 additional lesion amenable to biopsy. This/these lesion(s) should not be injected with study drug. |
| 3. | Any number of prior systemic therapies. |
| 4. | ECOG Performance status 0-1. |
| 5. | Laboratory parameters:<br>• Absolute neutrophil count (ANC) ≥ 1000/mm$^3$;<br>• Platelets ≥ 100,000/mm$^3$;<br>• Hemoglobin (Hgb) ≥ 9 g/dL;<br>• Hgb-A1C ≤ 7.5%;<br>• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN);<br>• Bilirubin ≤ 2.5 × ULN (≤ 4 × ULN for subjects with Gilbert's disease);<br>• Alkaline phosphatase ≤ 2.5 × ULN;<br>• Creatinine ≤ 1.5 × ULN;<br>• International normalized ratio (INR) or prothrombin time (PT) AND activated partial thromboplastin time (aPTT)/PTT ≤1.5 X ULN. NOTE: for subjects on therapeutic anticoagulation, subject must be stable on current regimen, as determined by the Investigator. |
| 6. | Age ≥ 18 years. |
| 7. | Able and willing to give valid written informed consent. |

## 5.2 Exclusion Criteria

*Subjects **may not** enter the study if they fulfill any of the following criteria:*

| | |
|---|---|
| 1. | Prior treatment with combination CTLA-4 and PD-1/PD-L1 blockade, with the exception of subjects with melanoma. |
| 2. | Participants may not have been treated intratumorally with polyICLC. |
| 3. | Unresolved irAEs following prior biological therapy, except that stable and managed irAEs may be acceptable (e.g., hypothyroidism or hypopituitarism on appropriate replacement). |
| 4. | Subjects with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, seizures not controlled with standard medical therapy, any active brain metastases, or, within 6 months of the first date of treatment on this study, history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage. |
| 5. | Subjects with clinically significant cardiovascular disease, including:<br>a. Uncontrolled hypertension, defined as systolic blood pressure (BP) > 150 mmHg or diastolic BP > 90 mmHg.<br>b. Myocardial infarction or unstable angina within 6 months of the first date of treatment on this study. |

| | |
|---|---|
| | c. History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or cardiac arrhythmias requiring anti-arrhythmic medications, except for atrial fibrillation that is well controlled with anti-arrhythmic medication.<br>d. Baseline ejection fraction ≤ 50% as assessed by echocardiogram or multi-gated acquisition (MUGA) scan.<br>e. New York Heart Association (NYHA) Class II or higher congestive heart failure.<br>f. Grade 2 or higher peripheral ischemia [brief (< 24 hours) episode of ischemia managed non-surgically and without permanent deficit]. |
| 6. | History of pneumonitis or interstitial lung disease. |
| 7. | Active, suspected or prior documented autoimmune disease (including but not restricted to inflammatory bowel disease, celiac disease, Wegner's granulomatosis and Hashimoto's thyroiditis, etc.). Participants with vitiligo, alopecia, type I diabetes mellitus, residual hypothyroidism (e.g., following Hashimoto syndrome) due to autoimmune condition only requiring hormone replacement, psoriasis or any chronic skin condition not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects without active disease in the last 5 years may be included but only after consultation with the study physician. Subjects with celiac disease controlled by diet alone may also be included. |
| 8. | Other malignancy within 2 years prior to entry into the study, except for those treated with surgical therapy only (e.g., localized low-grade cervical or prostate cancers). |
| 9. | Subjects with clinical symptoms or signs of gastrointestinal obstruction and/or who require drainage gastrostomy tube and/or parenteral hydration or nutrition. |
| 10. | Known immunodeficiency or HIV, Hepatitis B, or Hepatitis C positivity. Antibody to Hepatitis B or C without evidence of active infection may be allowed. |
| 11. | History of severe allergic reactions to any unknown allergens or any components of the study drugs. |
| 12. | Other serious illnesses (e.g., serious infections requiring antibiotics, bleeding disorders). |
| 13. | Participation in any other clinical trial involving another investigational agent within 4 weeks prior to Day 1 of the study. |
| 14. | Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study. |
| 15. | Lack of availability for immunological and clinical follow-up assessment. |
| 16. | Women of child bearing potential who are pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) or nursing. |
| 17. | **Female subjects of childbearing potentia**l who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (see table below) from screening, and must agree to continue using such precautions through 90 days after the last dose of durvalumab or through 6 months after the last dose of durvalumab + tremelimumab (whichever is longer). Nonsterilized male partners of a female subject must use male condoms plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period |

| | |
|---|---|
| | is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.<br><br>Female subjects should refrain from breastfeeding (or pumping breast milk) throughout the period described above.<br><br>Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmeno-pausal.<br><br>Females will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:<br>• Females <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).<br>• Females ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy.<br><br>**Nonsterilized male subjects** who are sexually active with a female partner of childbearing potential must use male condoms plus spermicide from screening through 90 days after last dose of durvalumab or through 6 months after the last dose of durvalumab + tremelimumab (whichever is longer). Female partners (of childbearing potential) of a male subject must use a highly effective method of contraception (see table below) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.<br><br>Male subjects should refrain from sperm donation throughout the period described above.<br><br>Highly effective methods of contraception are described in the table below. 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).<br><br>Acceptable highly effective methods of contraception are described in the following table: |

<table>
<tr><td></td><td>
<table>
<tr><td colspan="2">Highly Effective[a] Methods of Contraception</td></tr>
<tr><td>Barrier/Intrauterine Methods</td><td>Hormonal Methods</td></tr>
<tr><td>• Copper T intrauterine device<br>• Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[b]</td><td>• “Implants”: Etonogestrel-releasing implants: e.g. Implanon® or Norplan®<br>• “Intravaginal devices”: e.g. Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing®<br>• “Injection”: Medroxyprogesterone injection: e.g. Depo-Provera®<br>• “Combined Pill”: Normal and low dose combined oral contraceptive pill<br>• “Patch”: Norelgestromin /ethinylestradiol-releasing transdermal system: e.g., Ortho Evra®<br>• “Minipill[c]”: Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette®</td></tr>
<tr><td colspan="2">a - Highly effective (i.e., failure rate of <1% per year)<br>b - This is also considered a hormonal method<br>c - Cerazette® is currently the only highly effective progesterone based pill</td></tr>
</table>
</td></tr>
<tr><td>18.</td><td>Any condition that, in the clinical judgment of the treating physician, is likely to interfere with the interpretability of the data or to prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.</td></tr>
<tr><td>19.</td><td>History of allogeneic organ transplant</td></tr>
<tr><td>20.</td><td>Subjects must not donate blood while on study and for at least 90 days following the last durvalumab treatment or for 6 months after the last dose of tremelimumab (whichever is longer).</td></tr>
</table>

## 5.3 Restrictions on Concomitant Therapies

### 5.3.1 Non-Permitted Concomitant Therapies

Subject **may not** receive the following concomitant therapies during the study, except as allowed in Section 5.3.2:

| | |
|---|---|
| 1. | Systemic treatment with high-dose glucocorticosteroids or other immunosuppressive treatments (e.g., methotrexate, chloroquine, azathioprine, adalimumab), with a wash-out period of 2 weeks prior to Day 1. |
| 2. | Other cancer therapy (e.g., drug, radiation, or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1. (6 weeks for nitrosoureas and 12 weeks for antibodies other than anti-CTLA-4 or anti-PD-1/PD-L1 antibodies). |
| 3. | Live/attenuated vaccines 1 month prior to Day 1 and for at least 6 months after the last dose of treatment. |
| 4. | Sunitinib within 3 months after the last dose of tremelimumab. |
| 5. | Drugs with laxative properties and herbal or natural remedies for constipation should generally be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea, but, for example, opiate-induced constipation may be treated with laxatives at the Investigator's discretion. |
| The wash-out period prior to Day 1 of the study for all non-permitted drugs should be at least 1 week, unless stated otherwise above. | |

### 5.3.2 Permitted Concomitant Therapies

*Subject **may** receive the following concomitant therapies during the study:*

| | |
|---|---|
| 1. | Inhaled or oral steroids for treating mild to moderate asthma or allergies; inhaled steroids (e.g., fluticasone propionate/salmeterol, triamcinolone acetonide) are permitted at low doses (< 500 µg fluticasone per day, or equivalent). |
| 2. | Nasal steroids or topical steroids for localized (< 5% of body surface area) dermatitis. |
| 3. | Replacement steroid doses in subjects with stable adrenal or pituitary insufficiency. |
| 4. | Non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, and specific COX-2 inhibitors. |
| 5. | Antihistamines and other non-steroidal anti-allergy medication. |
| 6. | Hormone or hormone-related anti-cancer therapy, and cancer supportive therapy such as bone modifying agents (bisphosphonates/RANK-L inhibitors). |
| 7. | At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids to treat durvalumab-related immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted; however, caution should be exercised and additional international normalized ratio (INR) monitoring is recommended. |
| All prescription and nonprescription drugs must be recorded in the concomitant medications section of the case report form, listing generic (preferably) or brand name, indication, dose, route, and dates of administration. All non-drug therapies must be recorded in the respective sections of the case report form. | |

# 6 Study Drug Preparation and Administration

All study drugs are manufactured in accordance with Good Manufacturing Practices (GMP).

**Order of Drug Administration**
Intravenous infusions will be administered first, followed by intratumoral injections. On days when both tremelimumab and durvalumab are to be administered IV, the durvalumab infusion will start at least 60 minutes after the end of the tremelimumab infusion. With respect to intratumoral injections, tremelimumab will be administered first followed by polyICLC.

## 6.1 Tremelimumab

Tremelimumab is supplied by the Sponsor. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. Please see Section 7.2.8 for additional details. See Section 6 for order of drug administration.

### 6.1.1 Tremelimumab Study Drug Information

| | | | |
|---|---|---|---|
| Manufacturer | MedImmune | | |
| Expiration/Retest Date | *Expiration/retest dates are documented on the QA Disposition of Investigational Medicinal Product (IMP) Report.* | | |
| Container Description | *Type:* Single-use vial | *Material:* Clear glass | *Size:* 20 mL |
| Formulation | Liquid solution containing 400 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5. | | |
| Active Ingredient Content | *Mass/Weight:* 400 mg/vial | *Volume:* 20 mL | *Concentration:* 20 mg/mL |
| Storage Conditions | +2°C to +8°C (36°F to 46°F). Do not freeze. | | |
| Labeling | Product name, lot number, and storage conditions | | |

Tremelimumab is also available in a 25 mg/vial format; the concentration remains 20 mg/mL.

| | | | |
|---|---|---|---|
| Manufacturer | MedImmune | | |
| Expiration/Retest Date | *Expiration/retest dates are documented on the QA Disposition of Investigational Medicinal Product (IMP) Report.* | | |
| Container Description | *Type:* Single-use vial | *Material:* Clear glass | *Size:* 2 mL |
| Formulation | Liquid solution containing 25 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5. | | |
| Active Ingredient Content | *Mass/Weight:* 25 mg/vial | *Volume:* 1.25 mL/vial | *Concentration:* 20 mg/mL |
| Storage Conditions | +2°C to +8°C (36°F to 46°F). Do not freeze. | | |
| Labeling | Product name, lot number, and storage conditions | | |

### 6.1.2 Tremelimumab Investigational Product Inspection

Each vial of tremelimumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately.

### 6.1.3 Tremelimumab for Intratumoral Injection

#### 6.1.3.1 Preparation and Administration of Tremelimumab for Intratumoral Injection

The volume of tremelimumab to be administered with each intratumoral injection will be 0.5 mL for a 10 mg dose and 0.15 mL for a 3 mg dose for all subjects who will receive tremelimumab. One syringe should be filled aseptically from 1 vial for each dose.

The intratumoral injections will be administered by a physician or nurse under physician supervision. For particularly large lesions (> 1 cm in longest diameter), the dose can be divided and administered into more than 1 quadrant of the lesion. For example, for most lesions, the needle can be moved within each quadrant of the lesion, or if the lesion is too large, separate injections will be given for the total dose (to cover more of the lesion). During injections, it is recommended that the investigator distribute the injectate throughout the lesion targeted. If the injected lesion regresses completely before all of the intratumoral injections are administered, no further intratumoral injections will be given. Alternatively, if the lesion is too small to inject the complete volume of intratumoral study drug, the dose may be divided among a maximum of 3 lesions. The same lesions must be injected with the same volume at each time point in each subject.

A physician must be present at the site or immediately available to respond to emergencies during administration of all investigational product(s). Fully functional resuscitation facilities should be available.

The subjects will be monitored before and for at least 1 hour after the intratumoral injections, including a determination of temperature, blood pressure, heart rate, and respiratory rate.

The total time between needle puncture of the tremelimumab vial to start of administration should not exceed 4 hours at room temperature, or 24 hours at 2°C to 8°C (36°F to 46°F). If tremelimumab administration has to be delayed, a new dose must be prepared from new vials.

Tremelimumab does not contain preservatives, and any unused portion must be discarded.

### 6.1.4 Tremelimumab for Intravenous Infusion

#### 6.1.4.1 Preparation of Tremelimumab for Intravenous Infusion

For dose preparation steps, the following ancillary items are required:

- IV infusion bags of 0.9% sodium chloride injection or 5% (w/v) dextrose. Infusion bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (e.g., polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP-free.
- IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate (TOTM) or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. Lines must contain a

0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone (PES) or polyvinylidine fluoride DRF (PVDF).
- Syringes made of polypropylene and latex-free.
- Needles made of stainless steel.

Preparation of tremelimumab and preparation of the IV bag are to be performed aseptically by the IP manager or designated personnel. No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed.

Tremelimumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. The IV bag size should be chosen such that the final concentration of tremelimumab after dilution in the bag is between 0.10 mg/mL and 10 mg/mL. The appropriate IV bag size should be chosen for the respective dose. For the 75 mg dose only, tremelimumab may be administered using a 250 mL IV bag.

Subjects will receive a fixed dose tremelimumab, regardless of weight.

The volume of tremelimumab required for a 75 mg dose is 3.75 mL. The volume of tremelimumab required for a 22.5 mg dose is 1.125 mL.

The corresponding volume of investigational product should be rounded according to institutional practice.

The investigational product manager or qualified personnel will be responsible for preparing the IV doses using the following steps:

- Add the required dose volume of tremelimumab to the IV bag; ensure the allowable concentration range stated above is maintained for the IV bag size.
- Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.

Tremelimumab does not contain preservatives and any unused portion must be discarded.

#### 6.1.4.2 Administration of Tremelimumab for Intravenous Infusion

Following preparation of the dose, tremelimumab will be administered according to the following guidelines:

- Tremelimumab must be administered at room temperature (25°C) by controlled infusion into a peripheral vein or central line.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available.
- Tremelimumab solution should not be infused with other solutions or medications.

- Tremelimumab must not be administered via IV push or bolus but as a slow IV infusion.
- The infusion lines should be attached only at time of use. Lines used for infusion during dose administration must be equipped with 0.22 or 0.2 µm in-line filters.
- The entire contents of the IV bag should be administered by IV infusion over approximately 60 (±5) minutes, using a 0.2, or 0.22-µm in-line filter.
- The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). If there are no requirements to slow, interrupt, or permanently stop the infusion, the anticipated infusion time to deliver each dose is anticipated to be 60 (± 5) minutes. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new IV bag must be prepared from new vials and the remaining dose is given.
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The date, start time, interruption, and completion time of tremelimumab administration must be recorded in the source documents.
- Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.5.
- See Section 8.3.1 for guidelines for infusion-related reactions.
- Tremelimumab does not contain preservatives and any unused portion must be discarded.

## 6.2 Durvalumab (MEDI4736)

Durvalumab is supplied by the Sponsor. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. Please see Section 7.2.8 for additional details.

See Section 6 for order of drug administration.

### 6.2.1 Durvalumab Study Drug Information

| **Liquid formulation for intravenous administration** | | | |
|---|---|---|---|
| Manufacturer | MedImmune | | |
| Expiration/Retest Date | *Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.* | | |
| Container Description | *Type:*<br>Single use vial | *Material:*<br>clear glass | *Size:*<br>10 mL |
| Formulation | Liquid solution containing 500 mg durvalumab per vial.<br>The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0. | | |
| Active Ingredient Content | *Mass/Weight:*<br>500 mg | *Volume:*<br>10 mL | *Concentration:*<br>50 mg/mL |
| Storage Conditions | 2°C to 8°C (36°F to 46°F) Do not freeze | | |

| | |
|---|---|
| Labeling | Product name, lot number, and storage conditions |

### 6.2.2 Durvalumab Investigational Product Inspection

Each vial of durvalumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately.

### 6.2.3 Preparation of Durvalumab for Intravenous Infusion

Preparation of durvalumab and preparation of the IV bag are to be performed aseptically by the IP manager or designated personnel. No incompatibilities between durvalumab and polyvinylchloride or polyolefin copolymers have been observed.

*Dose Calculation:*
Subjects will receive a fixed dose of durvalumab:

- **Starting dose: 1500 mg** Q4W
  **NOTE: The durvalumab dose of 1500 mg Q4W is for subjects > 30 kg.** If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.
- **Dose de-escalation: 750 mg** Q4W.

The volume of durvalumab (in mL) to be added to the IV bag is calculated as follows:

| | | | | |
|---|---|---|---|---|
| Volume of Durvalumab (mL) | = | Dose level (mg) | ÷ | Durvalumab Concentration (nominal 50 mg/mL) |

*Dose Preparation:*
Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2 or 0.22 µm in-line filter. The IV bag size should be chosen such that the final durvalumab concentration after dilution in the bag must be 1 mg/mL to 15 mg/mL. The appropriate IV bag size should be chosen for the respective dose.

The calculated volume of durvalumab is added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag; ensure the allowable concentration range stated above is maintained for the IV bag size.

The following examples are provided for a 250 mL bag.

*Example:*
For a 1500 mg dose, 30 mL of durvalumab is diluted in a 250 mL IV bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

For a 750 mg dose, 15 mL of durvalumab is diluted in a 250 mL IV bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Durvalumab does not contain preservatives; any unused portion must be discarded.

### 6.2.4 Durvalumab Administration

Following preparation of the dose, durvalumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during administration of all investigational product(s). Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- Durvalumab must not be administered via IV push or bolus but as an IV infusion.
- Durvalumab solution should not be infused with other solutions or medications.
- Durvalumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- The entire contents of the IV bag should be administered as an IV infusion over 60 (± 5) minutes, using a 0.2-µm in-line filter. **An infusion time of less than 55 minutes is considered a deviation.**
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new IV bag must be prepared from new vials and the remaining dose is given.
- The date, start time, interruption, and completion time of durvalumab administration must be recorded in the source documents.
- Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.5.
- See Section 8.3.1 for guidelines for infusion-related reactions.
- Durvalumab does not contain preservatives, and any unused portion must be discarded.

## 6.3 PolyICLC

See Section 6 for order of drug administration.

### 6.3.1 PolyICLC Study Drug Information

| | | | |
|---|---|---|---|
| Manufacturer | Oncovir | | |
| Expiration/Retest Date | *Expiration/retest dates are documented on the Certificate of Conformance.* | | |
| Container Description | *Type:*<br>Single-use unpreserved vial | *Material:* | *Size:*<br>1 mL |
| Formulation | PolyICLC is supplied in vials containing 1 mL of opalescent white suspension (approximately 2 mg/mL). Each mL of polyICLC for injection contains approximately 2 mg/mL poly-IC, 1.5 mg/mL poly-L-lysine, and 5 mg/mL sodium carboxymethylcellulose in 0.9% sodium chloride solution and adjusted to pH 7.6-7.8 with sodium hydroxide. | | |
| Active Ingredient Content | *Mass/Weight:*<br>approximately 2 mg | *Volume:*<br>1 mL | *Concentration:*<br>approximately 2 mg/mL |
| Storage Conditions | +2°C to +8°C (approximately 40°F) Do not freeze | | |
| Labeling | Product name, concentration, lot number, date of manufacture, manufacturer, and investigational use statement | | |

### 6.3.2 PolyICLC Investigational Product Inspection

Each vial of polyICLC selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the Investigator and Sponsor should be notified immediately.

### 6.3.3 PolyICLC Preparation and Administration

PolyICLC is supplied by the Ludwig Institute for Cancer Research in vials containing 1 mL of opalescent white suspension (approximately 2 mg/mL). PolyICLC is withdrawn from the vial under sterile conditions and is to be administered intatumorally or IM as supplied. It can also be diluted with normal saline. For both routes of administration (intratumoral and IM), the dose of polyICLC will be 1 mg.

PolyICLC does not contain preservatives, and any unused portion must be discarded.

NOTE:
Lot PJ215-1-10-01 of PolyICLC has a labeled concentration of 2 mg/mL. As the PolyICLC dose is 1 mg, this corresponds to 0.5 mL. Lot PJ215-1-10-01 expired on 28 FEB 2018 and was replaced by Lot PJ215B03.
Lot PJ215B03 has a concentration of 1.8 mg/mL. For a 1 mg dose using this lot, the volume to be administered is 0.556 mL (this number may be rounded according to institutional practice).

The volume administered for subsequent lots should be adjusted accordingly so that the administered dose is 1 mg.

**Intratumoral injection**

Intratumoral injections as scheduled will be administered by a physician or nurse under physician supervision at a dose of 1 mg. For particularly large lesions (> 1 cm in longest diameter), the polyICLC dose can be divided and administered into more than 1 quadrant of the lesion. For example, for most lesions, the needle can be moved within each quadrant of the lesion, or if the lesion is too large, separate injections will be given for a total dose of 1 mg (to cover more of the lesion). During injections, it is recommended that the investigator distribute the injectate throughout the lesion targeted. If the lesion is too small to inject the complete volume of intratumoral study drug, the dose may be divided among a maximum of 3 lesions. If the injected lesion regresses completely before all of the intratumoral injections are administered, no further intratumoral injections will be given unless the lesion grows again during the intratumoral injection period.

One syringe should be filled aseptically from 1 vial according to the directions above.

Pain medication to be administered includes, if needed, acetaminophen, diphenhydramine, benzodiazepines, and/or opiates. Other analgesics may be given at the discretion of the investigator.

Some degree of inflammatory response in the injected lesion is expected as part of the therapy. Prior to each intratumoral injection, the maximal diameter of peritumoral inflammation will be recorded in millimeters and photographically, if appropriate in the judgment of the investigator, as a baseline for subsequent post-injection measurements.

The subjects will be monitored before and for at least 1 hour after each of the intratumoral injections, including a determination of temperature, blood pressure, heart rate, and respiratory rate.

**IM Injection**

IM injections will be given using standard technique into the thighs or upper arms. Injection sites may be rotated based on subject and investigator preference and will be recorded in the electronic case report form (eCRF).

Subjects will be monitored before and for at least 1 hour after the first IM injection, including a determination of temperature, blood pressure, heart rate, and respiratory rate.

## 6.4 Estimated Drug Requirements

| Drug | Required Quantity (vials) |
|---|---|
| Durvalumab | 5703 |
| Tremelimumab | 713 |
| PolyICLC | 2326 |

## 6.5 Monitoring of Tremelimumab and Durvalumab IV Dose Administration

Subjects will be monitored before, during and after tremelimumab and durvalumab infusions with assessment of vital signs according to the table below:

| Vital Signs Assessment on Study Drug Administration Days | | | | | |
|---|---|---|---|---|---|
| **Drug** | **Pre Dose** | **During Infusion** | **End of Infusion (± 5 minutes)** | **30 (± 5) Minutes Post Infusion** | **60 (± 5) Minutes Post Infusion** |
| **Tremelimumab** | X | Every 30 (± 5) minutes | X | | |
| **Durvalumab** | X | Every 15 (± 5) minutes | X | X | X |

Note: When IV durvalumab and IV tremelimumab are to be administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even though vital signs assessment is not required during the entire 60-minute period post tremelimumab.

If a subject tolerates treatment well for the first 4 doses of durvalumab (i.e., no infusion reactions), subsequent infusions in that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

| Vital Signs Assessment on Study Drug Administration Days (after first 4 doses) | | | | |
|---|---|---|---|---|
| **Drug** | **Pre Dose** | **During Infusion** | **End of Infusion (± 5 minutes)** | **15 (± 5) Minutes Post Infusion** |
| **Durvalumab** | X | Every 30 (± 5) minutes | X | X |

## 6.6 Drug Overdose Management

There are no known antidotes available for tremelimumab, durvalumab, or polyICLC. Any overdoses with these drugs should be managed symptomatically. An overdose is defined as a subject receiving any dose in excess of that specified in this protocol by > 10%. All such overdoses must be reported, with or without associated AEs/serious adverse events (SAEs), according to Section 7.1.2.2.

# 7 Administrative, Legal and Ethical Requirements

## 7.1 Documentation and Reporting of Adverse Events

### 7.1.1 General AE/SAE Definitions per ICH Guidelines

An **Adverse Event (AE)** is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the 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 (investigational) product, whether or not related to the medicinal (investigational) product.

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of LICR studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods.,

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

1. Results in death,
2. Is life-threatening[A],
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition[B].

[A] The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

[B] Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 7.1.2 Additional Expedited Reporting Requirements for this Study

For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (see Section 7.1.6 for Sponsor contact information) and may result in submission of an SAE based on certain criteria outlined below:

1. Pregnancy
2. Overdose (as defined in Section 6.6)
3. Hepatic Function Abnormality (as defined in Section 7.1.8).
4. New cancers
5. Deaths

#### 7.1.2.1 Pregnancy

##### 7.1.2.1.1 Maternal Exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer) (see Section 5.2, #17).

If a subject becomes pregnant during the course of the study, the study drugs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs (see section 7.1.6). 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 subject was discontinued from the study.

If any pregnancy occurs in the course of the study, the Investigator or other site personnel should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

##### 7.1.2.1.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer) (see Section 5.2, #17).

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last drug 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 subject'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.

#### 7.1.2.2 Overdose

Any overdose (as defined in Section 6.6) of a study subject, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to the Sponsor. If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. 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 according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of the study drugs. The Investigator will use clinical judgment to treat any overdose. See Section 6.6 for additional details.

#### 7.1.2.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 7.1.8) 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, 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 MedImmune/AstraZeneca.

#### 7.1.2.4 New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the subject's inclusion in this study.

#### 7.1.2.5 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period (On Study Follow-up) after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should be reported as an SAE if it meets SAE reporting criteria per Section 7.1.6.

- 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 the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the eCRF.
- The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to LICR within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented only in the Post Study Follow-up eCRF form. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

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

### 7.1.3 Severity of an Adverse Event

The severity of all serious and non-serious adverse events should be assessed according to the National Cancer Institute CTCAE Scale (Version 4.03).

### 7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents", NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is *clearly related* to the investigational agent)
Probably related (The AE is *likely related* to the investigational agent)
Possibly related (The AE *may be related* to the investigational agent)
Unlikely related (The AE is *doubtfully related* to the investigational agent)
Unrelated (The AE is *clearly not related* to the investigational agent)

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in Section 1 (Background) of this protocol may support these evaluations.

### 7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur:

a. from the date of signing the informed consent, and
b. until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment).

Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).

### 7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

**In addition to the General Reporting Requirements specified in Section 7.1.5, all events meeting the criteria for an SAE as per Section 7.1.1, irrespective of suspected causation, must be reported by the Investigator to the Sponsor's Drug Safety Contact (primarily) or, alternatively, to the Primary Sponsor Contact, within 24 hours of becoming aware of the event (see contact information below). SAEs should be reported via the Medidata RAVE data capture system (which utilizes "Safety Gateway"), using the respective Adverse Event and Safety Case Summary eCRFs. This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. In the event that the SAE cannot be reported via Medidata RAVE, the SAE should be reported using the "Initial Serious Adverse Event Report Form," provided by the Sponsor.**

**Note: If an SAE cannot be reported via Medidata RAVE or the "Initial Serious Adverse Event Report Form" within 24 hours of becoming aware of the event, the Sponsor's Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, must be contacted by phone or email within 24 hours of becoming aware of the event. In this case, the phone or email notification can then be followed up through Medidata RAVE or an "Initial Serious Adverse Event Report Form" within one working day of the event.**

If the "Initial Serious Adverse Event Report Form" is being used, the expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact. Studies utilizing Medidata RAVE (and the "Safety Gateway") built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to Medidata RAVE and "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below for contact information).

**In urgent cases, pre-notification via phone or informal e-mail should be considered.**

| *Drug Safety Contact:* | *Primary Sponsor Contact:* |
|---|---|
| [redacted]<br>Senior Manager, Drug Safety<br>Clinical Trials Management<br>Ludwig Institute for Cancer Research<br>600 3rd Ave Floor 32<br>New York, New York 10016<br>[redacted] | [redacted]<br>Senior Director<br>Clinical Trials Management<br>Ludwig Institute for Cancer Research<br>600 3rd Ave Floor 32<br>New York, New York 10016<br>[redacted] |

Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned a serious adverse event tracking number by the Sponsor. Institutional Review Boards may have specific rules on which Adverse Events need to be reported expeditiously, as well as, the time frames for such reporting.

SAE Reports will be evaluated by the Sponsor's Medical Monitor. Regulatory authorities and other investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug(s) cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 Calendar days.

Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement.

### 7.1.7 Serious Adverse Event (SAE) Follow-up Requirements

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available, using the "SAE Follow-up Report form", provided by the Sponsor.

### 7.1.8 Adverse Events of Special Interest (AESIs)

An adverse event of special interest (AESI) is an event of scientific and medical interest specific to understanding of the investigational products and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid recording of all AEs including AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the investigational products.

AESIs for durvalumab 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 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 AE being an irAE, the Investigator should promptly contact the Medical Monitor.

**If an AESI also meets SAE criteria, the event will be reported as an SAE per Section 7.1.6.**

**AESIs observed with durvalumab and tremelimumab and those considered AESIs for the purpose of this study are listed below.** Further information on these AESIs (e.g. presenting symptoms) can be found in the current versions of the durvalumab (MEDI4736) and tremelimumab Investigator's Brochures. Guidelines for the management of subjects experiencing toxicities for durvalumab and tremelimumab can be found in Section 8.3 and in the following Medimmune guideline: ***"Medimmune's Dosing Modification and Toxicity Management Guidelines for Immune- mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."***

- **Diarrhea/Colitis and Intestinal Perforation**

  Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with study medications. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.

- **Pneumonitis/Interstitial Lung Disease (ILD)**
  Adverse events of pneumonitis have been observed with anti-PD-1, and anti-PD-L1 antibodies (see IB). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is required.

- **Hepatic Function Abnormality (Hepatitis / transaminase increases)**
  Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (see IB). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g.,

cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Cases where a subject shows an AST or ALT ≥ 3 x ULN or total bilirubin ≥ 2 x ULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

- **Neurotoxicity (Neuropathy / neuromuscular toxicity)**
  Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.

- **Endocrine Disorders**
  Immune-mediated endocrinopathies include hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism, and Type 1 diabetes mellitus.
  **Type 1 diabetes mellitus:** For subjects with suspected diabetes mellitus, Investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.

- **Dermatitis/Rash**
  Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.

- **Nephritis and increases in Serum Creatinine**
  A consult with a Nephrologist should be done as well as monitoring for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.). Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.). Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

- **Pancreatic Disorders**
  Immune-mediated pancreatitis includes autoimmune pancreatitis or labs suggestive of pancreatitis (increased serum lipase, increased serum amylase).

- **Myocarditis**
  Myocarditis, a rare, but severe immune-mediated adverse event, presents with signs/symptoms such as decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block. For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection).

- **Myositis /Polymyositis**
  Myositis or polymyositis should be suspected in patients who present with proximal muscle weakness and the evaluation should include an examination of the skin, muscle enzyme measurement, antibody testing, any systemic disease manifestations and exclusion of other diseases including drug-induced myopathy. Cases of myositis have been reported with myocarditis in which immune infiltration has been described in skeletal and cardiac muscle (see IB).

- **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.
- **Hypersensitivity and Infusion Reactions**
  Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (see IB). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines and/or literature for the management of subjects experiencing the toxicities for durvalumab and tremelimumab can be found in Section 8.3.

Guidelines for the management of subjects experiencing toxicities for PolyICLC can be found in Section 8.4.

## 7.2 Administrative Sponsor Requirements

### 7.2.1 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system ("Study Master File") of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

### 7.2.2 Case Report Form Data Collection

Electronic Case Report Forms (eCRF) will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigator will sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the CRF and will certify its content.

### 7.2.3 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood and be in the language appropriate for the trial site.

### 7.2.4 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site qualification, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other sponsor staff will meet with the investigator staff and require direct access to source data/documents. Such access may also be required for Institutional Review Board review, and regulatory inspection/audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the case report forms at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor should have access to subject charts, laboratory reports and other subject records needed to verify the entries on the case report forms ("source data verification").

### 7.2.5 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects do usually not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the sponsor if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

### 7.2.6 Premature Subject Withdrawal from Treatment or from Study

A subject may withdraw from study treatment or from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from treatment or from the study. Specific subject withdrawal reasons are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw from study treatment or from the study, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

A complete final evaluation should be made at the time of the subject's withdrawal, the appropriate form in the case report form should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

### 7.2.7 Early Trial Termination

"End of study" is defined as the last visit of the last subject. Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The investigator must also notify the appropriate Institutional Review Board accordingly.

### 7.2.8 Study Drug Shipments and Accountability

Study drug shipments will be addressed to the Principal Investigator's authorized designee, preferably the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject's identification (subject number and code)
- date and quantity of drug dispensed
- date and quantity of drug returned to the investigator/pharmacy (if applicable)
- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for the accounting of all used and unused trial supplies. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

## 7.3 Regulatory, Legal, and Ethical Requirements

### 7.3.1 Good Clinical Practice (GCP), Laws and Regulations

The investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

### 7.3.2 Informed Consent

The investigator must obtain witnessed (if applicable) written informed consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study-specific procedures are performed. The subject should be given a copy of the informed consent documentation. The original signed and dated informed consent form must be retained in the study records at the study site and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

### 7.3.3 Institutional Review Board

The investigator must obtain written approval from the appropriate Institutional Review Board for the protocol and informed consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The investigator must report Serious Adverse Events (SAEs) to the appropriate Institutional Review Board in accordance with the Institutional Review Board's rules and guidelines (see also Section 7.1).

The investigator must assure that continuing review (at least once per year) of the study is performed by the Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the investigator must provide study reports on an annual basis and upon completion of the study.

All correspondence with, and reports to, the Institutional Review Board must be maintained in the study files at the study site and copies must be sent to the Sponsor.

### 7.3.4 Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the case report forms or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the informed consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

# 8 Appendices

## 8.1 Protocol Version History

**Original issue**
**Issue date: 10-NOV-2015**
**Summary of Changes:** n/a

**Amendment 001**
**Issue date: 08-FEB-2016**
**Summary of Changes:**
The following changes were made:

1. Administrative changes: General spelling, capitalization, abbreviation, and formatting changes, as needed.
2. Synopsis, Section 3.1 and Section 6.1.3.1: the word "randomized" was deleted, as this is not a randomized study.
3. Synopsis, Table 1, and Section 3.1.7.2: "60 evaluable subjects" was changed to "66 evaluable subjects" to correct an inconsistency with Section 3.1.5.
4. Section 3.1.3: "will be" was changed to "is."
5. Section 3.1.6: Phase 2 sample size language was clarified by the addition of the following: "The expansion phase sample size of 66 subjects is deemed to be sufficient for the assessment of safety and tolerability as it provides sufficient precision for estimation of adverse events. The confidence intervals (CI) for estimating the incidence of AEs ranging from 10% to 90% (in increments of 10%) are listed below. The margins of error (half width of the CI) are deemed acceptable for the estimation of AE incidences in this early phase trial." The following table was inserted:

| Number of Subjects with Event | Incidence | 95% Confidence Interval (Normal approximation) | Margin of error (half width of the CI) |
|---|---|---|---|
| 7/66 | 0.1 | (0.028, 0.172) | 0.072 |
| 14/66 | 0.2 | (0.103, 0.297) | 0.097 |
| 20/66 | 0.3 | (0.189, 0.411) | 0.111 |
| 27/66 | 0.4 | (0.282, 0.518) | 0.118 |
| 33/66 | 0.5 | (0.379, 0.621) | 0.121 |
| 40/66 | 0.6 | (0.482, 0.718) | 0.118 |
| 47/66 | 0.7 | (0.589, 0.811) | 0.111 |
| 53/66 | 0.8 | (0.703, 0.897) | 0.097 |
| 60/66 | 0.9 | (0.828, 0.972) | 0.072 |

6. Section 3.1.16: The following clarification was added to the last paragraph: "The first Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) since the last study visit. If the first Post Study Follow-up is less than 90 days since the last administration of study drug, any irAEs occurring since the last study visit will continue to be collected and recorded at the subsequent Post Study Follow-up visit."

7. Section 3.2 : Study flowchart was updated to add amylase and lipase to the assessments. In addition, Free T3, Free T4, and TSH were moved to a separate line for clarification, as these assays are not part of the routine chemistry analysis.
8. Section 4.1.2: Additional detail was inserted for evaluation and statistics: "Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity (according to CTCAE version 4.03) and relationship to study medication. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point."
9. Section 4.2.2: The phrase "will be conducted for Cohort 2 and" was deleted from the first sentence in order to provide consistency with Section 4.0.
10. Section 5.1:
    - Inclusion Criterion #1 was clarified to require that subjects have unresectable disease, have failed at least one standard of care therapy, and do not have curative options. Changes in bold: "Subjects must have histologic confirmation of advanced **unresectable disease, have failed at least one standard of care therapy, and do not have curative options. Tumors should be** biopsy-accessible, measurable cancers of the following histologies:…"
    - # 4 – "ECOG" was added to Performance Status
11. Section 8.3.1:
    - Paragraph 3: deleted the reference to "Tremelimumab Guidelines for the Management of Diarrhea and Colitis" as this guideline is currently included in "Medimmune's Dosing Modification and Toxicity Management Guidelines."
    - Paragraph 4, which referenced the package inserts for ipilimumab, nivolumab, and pembrolizumab, was deleted.

**Amendment 002**
**Issue date: 12-APR-2016**
**Summary of Changes:**
The following changes were made:

1. Changed IND # from 118511 to 130529.
2. Section 3.1.6: The following text was added: "The primary endpoint for the Phase 1 portion of the study is safety. The objective for Phase 1 is to determine the recommended combination dose (RCD). In each of the Phase 1 cohorts, a 3+3 design is used. Each cohort will be evaluated on its own. The only modification to the design is that the protocol evaluates up to 2 dose levels and starts at the desired dose level (Level 0). As only one drug is being modified in each cohort, the principles of a 3+3 design are applicable. The RCD for each cohort is defined as the highest dose level at which no more than 1 of 6 subjects experience DLTs. The Cohort 1A doublet (durvalumab +

polyICLC) will be enrolled first, starting at Level 0. Dose Level -1 will only be evaluated if Level 0 exceeds the RCD. Once safety is demonstrated for the subjects in the Cohort 1A doublet, the Cohort 1B triplet (durvalumab + polyICLC + tremelimumab IV) and the Cohort 1C triplet (durvalumab + polyICLC + intratumoral tremelimumab) will open to enrollment. Based on the DLT assessment, the starting dose Level 0 will either be expanded to 6 subjects or the dose level will be reduced to Level -1. This is in accordance with a standard 3+3 design, whereby a dose level may be reduced as well as escalated based on the DLTs observed. The table below gives the probabilities of dose expansion of dose Level 0 or de-escalation to dose Level -1 based on true DLT rate in the 3+3 design.

| | True DLT rate | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Probability of de-escalation | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% |
| | 0.91 | 0.71 | 0.49 | 0.31 | 0.17 | 0.08 | 0.03 | 0.01 | 0.001 |

Adverse events will be summarized by maximum toxicity grade for each dose level cohort. Phase 1 will enroll up to 36 subjects to determine the RCD. Once the RCD of the triplet dosing regimen has been determined in Cohort 1C, up to 66 subsequent subjects will be enrolled into the Phase 2 cohort at the RCD according to Cohort 1C. If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2. For the Cohort 1A doublet, if dose Level -1 is too toxic, the RCD cannot be determined and the study will stop. Otherwise, Cohorts 1B and 1C triplets will open in parallel at the doublet RCD of Cohort 1A, and the triplet RCD will be determined in both Cohorts 1B and 1C. If no triplet RCD can be determined, Phase 2 of the study will be done at the Cohort 1A doublet RCD. If triplet RCDs are determined for both Cohorts 1B and 1C, the triplet RCD of Cohort 1C will be used in Phase 2. If a triplet RCD can only be determined in Cohort 1B, that triplet RCD will be used in Phase 2. Phase 2: The phase 2 portion of the study is intended to indicate proof of concept regarding the activity of the combination selected in Phase 1, in a study of 8 disease types. The goal is to determine if there is any evidence to support future larger clinical trials of specific tumor targets. Enrollment of 6 subjects per tumor type will be allowed initially, with enrollment of an additional 6 subjects being contingent on at least one response among the initial 6 subjects. Response is defined in this protocol as achieving a partial response (PR) or complete response (CR) by immune-related RECIST or RECIST 1.1, or stable disease (SD) for at least 6 months. PD-1 receptors and PD-1 ligand have been previously investigated in Phase 1 and 2 studies. Response rates range from 8% to 25% overall, and from 10% to 35% in the squamous subpopulation (44). This combination therapy trial seeks to improve on these response rates. The stopping rule for lack of sufficient efficacy in the initial 6 subjects for each tumor type, results in a rejection rate of <20% if the true response rate for a particular tumor type is 25%. A total of (8)(6)= 48 subjects will be initially enrolled for the Phase 2 portion plus a potential additional (3)(6)= 18 subjects for three tumor types having at least one response in the initial group (total of 48+18= 66 subjects). For tumor types accruing 6+6= 12 subjects, an exact 90% confidence interval for response rate will be computed. The safety of the regimen taken into Phase 2 will be evaluated by the Medical Monitor on an ongoing basis. When 6 subjects have been enrolled and treated in a disease cohort, a review of the data from the cohort will be conducted by the internal data safety monitoring panel and a decision (based on

efficacy as well as safety) will be made whether to expand the disease cohort to 12 subjects. At any time during the study, the Medical Monitor and/or the internal data safety monitoring panel may stop the cohort or the study if the toxicity seen is not acceptable. Respective study stopping rules are described in Section 3.1.14 of the protocol. If more than one subject in the initial group of 6 subjects in a disease type have a DLT, then accrual to that disease type cohort will be terminated."

3. Section 3.1.7.2: Added phrases (changes in bold): Cohort 2 will expand the cohort that was treated at the RCD from the dose-finding phase. Up to 6 subjects per tumor type will be initially enrolled into Cohort 2. Data from all subjects who are treated with the dosing regimen in either the cleared dose-finding cohort or Cohort 2 will be reviewed **for safety/efficacy** to select up to 3 tumor types that demonstrate an efficacy signal, defined as at least 1 of 6 subjects within a tumor type who achieve a partial response (PR) or complete response (CR) by immune-related RECIST (irRECIST) or RECIST 1.1, or stable disease (SD) for at least 6 months (**See Section 3.1.6 regarding DLT assessment during expansion)**.
4. Section 3.1.10:
   - Treatment withdrawal criterion #6 "Initiation of alternative anti-cancer therapy including another investigational agent" was moved to Study withdrawal criterion #2 and changed to "Initiation of alternative anti-cancer therapy (marketed or investigational)."
   - The following phrase was removed from Study withdrawal criterion #1: "e.g., start of new treatment."
5. Section 3.1.13: Deleted "No formal interim analysis will be performed." Added "(see Section 3.1.6)" for analysis of Cohort 2.
6. Section 3.1.15.2: updated as follows:

| | |
|---|---|
| Duration of Study per Subject: | Up to 12 months treatment + 3 months On Study Follow-up |
| Enrollment Period: | 24 months |
| Length of Study: | 39 months (not including Post Study Follow-up as described in Section 3.1.16) |

7. Section 3.1.16: Next to last paragraph was changed **FROM:** "The first Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) since the last study visit. If the first Post Study Follow-up is less than 90 days since the last administration of study drug, any irAEs occurring since the last study visit will continue to be collected and recorded at the subsequent Post Study Follow-up visit." **TO:** "The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug."
8. Section 3.2, Flowchart:
   - "pre-existing symptoms" was deleted from the Medical History line
   - "Procedures" was added to the Concomitant medications line
   - Mg was added to the list of chemistry analytes
   - Vital signs assessments were added to all intratumoral polyICLC and first IM polyICLC injections
   - The following assessments were deleted: IV tremelimumab PK, IV durvalumab PK, tremelimumab/durvalumab ADA

- Footnote 6 (collected pre-dose and end of infusion) was deleted
- New Footnote 6 was added for AEs: "See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration."
- Footnote 9 (optional) was deleted and a new Footnote 9 was added: "Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
- Footnote 10 was added for Vital signs: "See Section 6.5 for assessment before/during/after IV infusions; Section 6.1.3.1 for intratumoral tremelimumab vitals assessments; Section 6.3.3 for intratumoral and IM polyICLC vitals assessments."

9. Section 4.3, Pharmacokinetics: all language pertaining to durvalumab and tremelimumab PK assessments pre and post respective IV infusions was deleted. PK assessments pre and post intratumoral tremelimumab were retained.
10. Section 4.4, Durvalumab and tremelimumab immunogenicity was deleted; other sections were re-numbered accordingly.
11. Section 5, Subject Eligibility: the following was added "NOTE: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
12. Section 5.2:
    - Exclusion Criterion #17: updated contraception language according to current language provided by AstraZeneca.
    - contraception requirements were changed from 6 months after last dose of drug to "90 days after last dose of durvalumab or 6 months after the last dose of tremelimumab (whichever is longer)
13. Section 5.3.1:
    - Added bold phrase to #2: "Wash-out period: 4 weeks **or 5 half-lives (whichever is shorter)** prior to Day 1."
    - Added the following as #5: "Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea."
14. Section 6.1.3.1:
    - 2nd paragraph, 5th sentence was changed as follows (changes in bold): "If the injected lesion regresses completely before all of the ~~**priming**~~ intratumoral injections are administered, no further intratumoral injections will be given."
    - 4th paragraph was changed as follows (changes in bold): The subjects will be monitored **before and** for at least 1 hour after the intratumoral injections, including a determination of **temperature,** blood pressure, heart rate, and respiratory rate. ~~**before and after injection**~~
15. Sections 6.1.4.2 and 6.2.4: infusion time for tremelimumab and durvalumab, respectively, were changed from 60 ± 10 minutes to 60 ± 5 minutes. The following statement was added: "An infusion time of less than 55 minutes is considered a deviation."
16. Section 6.3.3:
    - Intratumoral injection, 1st paragraph, last sentence was changed as follows (changes in bold): "If the injected lesion regresses completely before all of the ~~**priming**~~ **Intratumoral** injections are administered, no further intratumoral injections will be

given unless the lesion grows again **during the intratumoral injection period ~~or until Cycle 2 if the lesion regresses during Cycle 1.~~**

- Intratumoral injection, last paragraph was changed as follows (changes in bold): "The subjects will be monitored **before and** for at least 1 hour after each of the **~~first two~~** intratumoral injections **~~in each cycle,~~** including a determination of **temperature**, blood pressure, heart rate, and respiratory rate **~~before and after injection.~~**
- IM injection, 2nd paragraph was changed as follows (changes in bold): "Subjects will be monitored **before and** for at least 1 hour after the first IM injection, including a determination of **temperature**, blood pressure, heart rate, and respiratory rate **~~before and after the injection.~~**

17. Section 6.5: The following was added: "If a subject tolerates treatment well for the first 4 doses of MEDI4736 (i.e., no infusion reactions), subsequent infusions in that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

| **Vital Signs Assessment on Study Drug Administration Days (after first 4 doses)** | | | | |
|---|---|---|---|---|
| **Drug** | **Pre Dose** | **During Infusion** | **End of Infusion (± 5 minutes)** | **15 (± 5) Minutes Post Infusion** |
| **Durvalumab** | X | Every 30 (± 5) minutes | X | X |

18. Section 7.1.2: updated language according to current recommendations from MedImmune/AstraZeneca. Defined additional expedited reporting requirements for study, specifically pregnancy, overdose, and hepatic function abnormality
19. Section 7.1.5: language for documenting AEs was changes **FROM:** "Documentation of serious and non-serious adverse events includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as the causal relationship between the event and the study drug in accordance with Section 7.1.4. All serious and non-serious adverse events occurring between the date of signing the informed consent and the off-study date must be documented in the source records and on the respective section of the CRF, regardless of the assumption of a causal relationship. During the On Study Follow-up period, all AEs will continue to be documented for 90 days after the last dose of study drug." **TO:** "**"**All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur: a) from the date of signing the informed consent, and b) until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment).Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy)."
20. Section 7.1.6: Additional detail and clarification were added regarding reporting of SAEs to the Sponsor within 24 hours**.**

21. Section 7.1.8: Updated AESI language in the entire section according to current recommendations from MedImmune/AstraZeneca.
22. Section 7.2.2: the following statement was added: “All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.”
23. Section 8.3.1: Durvalumab and tremelimumab dose modifications for all other AEs (last portion of table) was changed as follows:
    - Grade 3 was separated from Grade 2 modifications
    - Grade 3 modifications were added: "Hold M and T. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume M and T administration at next scheduled dose. Otherwise, discontinue M and T permanently.”
    - Grade 4, bullet 2: the phrase ”in consultation with the Sponsor” was added.
24. Section 8.3.2:
    - For Point 2, “7 days or less” was changed to “≤ half the planned dosing interval.”
    - For Point 3, “7 days“ was changed to “half the planned dosing interval.”
25. Added a new Section 8.7, ECOG PS; other sections were re-numbered accordingly.
26. Administrative:
    - Spelling, grammar and typographical errors were corrected.
    - Formatting/administrative changes were implemented, as applicable.
    - Updated List of abbreviations
    - Monitor and Study Monitor were standardized as “Clinical Monitor” in Sections 7.2.4 and 7.2.8.

**Amendment 2.1 (Administrative Change)**
**Issue date: 05-MAY-2016**
**Summary of Changes:**

1. Section 3.1.6: Typographical errors were corrected in the table showing probability of de-escalation. Specifically, the text and table were changed as follows:

**FROM:**
The table below gives the probabilities of dose expansion of dose Level 0 or de-escalation to dose Level -1, based on true DLT rate in the 3+3 design.

| | True DLT rate | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% |
| Probability of de-escalation | 0.91 | 0.71 | 0.49 | 0.31 | 0.17 | 0.08 | 0.03 | 0.01 | 0.001 |

**TO:**
The table below gives the probabilities of de-escalation to dose Level -1, based on true DLT rate in the 3+3 design.

| | True DLT rate | | | | | | |
|---|---|---|---|---|---|---|---|
| | 10% | 20% | 30% | 40% | 50% | 60% | 70% |
| Probability of de-escalation | 0.09 | 0.29 | 0.51 | 0.69 | 0.83 | 0.92 | 0.97 |

| |
|---|
| **2.** Section 7.1.6: Changed Primary Sponsor Contact from [redacted] to [redacted]. |
| |
| **Amendment 3**<br>**Issue date: 16-May-2016**<br>**Summary of Changes:**<br>1. An administrative change was incorporated and documented as Amendment 2.1 (see above).<br>2. Section 3.1.2: Clarified that alternating enrollment will be used for Cohorts 1B and 1C (changes in bold): "After safety is demonstrated in the first 3-6 subjects in Cohort 1A, Cohorts 1B and 1C will open ~~to~~ **with alternating** enrollment."<br>3. Sections 3.1.7, 6.1.3.1, and 6.3.3: clarified that a maximum of 3 lesions may be injected with intratumoral tremelimumab and intratumoral polyICLC per patient per dose.<br>4. Section 3.1.7: The following statement was added: "See Section 6 for the sequence of drug administration on dosing days when multiple drugs are given."<br>5. Section 3.1.9, Dose limiting toxicity: Deleted the last 2 exceptions for item #3 (i.e., deleted "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." and "Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both investigator and sponsor."<br>6. Section 3.1.10: added the following NOTE to provide criteria that must be met to continue treatment until confirmation of progression of disease: " NOTE: Subjects meeting criteria for radiographic progression by RECIST 1.1 (Section 8.5) will be allowed to continue on therapy until confirmation of progression if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:<br>a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;<br>b. No significant decline in ECOG performance status;<br>c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.<br>7. Section 3.2, Study Flowchart:<br>1. Added Footnote 11 for disease assessments: "Subsequent imaging at 4 to 6 weeks after first documentation of RECIST v1.1-defined progression must be performed."<br>2. ECOG PS as a single assessment at baseline was deleted and ECOG PS assessments were added to Physical Examination assessments.<br>8. Section 4.2.1: added the following: "Disease assessments will be done in accordance with the flowchart in Section 3.2. Subsequent imaging at 4 to 6 weeks after first documentation of RECIST v1.1-defined progression must be performed."<br>9. Section 4.2.1.1: Clarified the ORR definition (changes in bold): "ORR is defined as the percentage of evaluable subjects meeting criteria of CR or PR ~~**by the end of 1 year**~~, **confirmed at a subsequent time point (≥ 4 weeks).**<br>10. Section 5.1, Inclusion Criteria, added the definition of biopsy-accessible tumor to #1:<br>• NOTE 1: A biopsy-accessible lesion is defined as a tumor lesion which can be, in the opinion of the Investigator or that of consulting physicians, safely accessed for |

biopsy or for injection by means of physical examination or imaging guided means such as ultrasound or CT scan (e.g., cutaneous lesions, inguinal nodes, supraclavicular or cervical nodes, superficial abdominal lesions, and lesions that are accessible by ultrasound guidance and not impacting vital organs/structures).
- References were added to Sections 1.1, 3.1 and 3.1.4 regarding the definition for a biopsy-accessible tumor/lesion.

11. Section 5.1, Inclusion Criteria: added the following to #5:
    - International normalized ratio (INR) or prothrombin time (PT) AND activated partial thromboplastin time (aPTT)/PTT ≤1.5 X ULN. NOTE: for subjects on therapeutic anticoagulation, subject must be stable on current regimen, as determined by the Investigator

**Amendment 4**
**Issue date: 20-AUG-2018**
**Summary of Changes:**

1. Synopsis: the following footnote was added to the table: "Q4W = every 4 weeks; IV = intravenous; ITM = intratumoral; IM= intramuscular. Note: See Section 3.1.7.1 for durvalumab doses for instances when a subject's body weight drops to ≤ 30 kg while on the study."
2. Section 2 (Study Rationale): The following paragraph was added to address the added requirement of weight-based durvalumab dosing for subjects whose body weight drops to ≤ 30 kg while on the study: "The 1500 mg Q4W dosing of durvalumab is recommended only for subjects with > 30 kg body weight in order to limit endotoxin exposure. See Section 3.1.7.1 for details regarding durvalumab dose requirements for instances when a subject's body weight drops to ≤ 30 kg while on the study. See Section 3.1.7.1 for additional details regarding the dose de-escalation cohorts for durvalumab and tremelimumab."
3. Section 3.1.7.1 (Phase 1: Dose-finding Cohorts):
    - Table 2: added clarification that the RCD for Cohorts 1B and 1C is the RCD from Cohort 1A; added footnote. This change was also implemented in the Synopsis.
    - The durvalumab dosing requirements were added for subjects whose body weight drops to ≤ 30 kg while on the study.
4. Section 3.1.8 (Dosing Adjustments, Delays and Discontinuations). The following paragraph was added: "If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline (i.e., the guideline that provides for the greatest dose reduction, dose delays or holds) should be followed. "
    - This paragraph was also added to Sections 8.3 and 8.4.
5. Section 3.1.9 (dose-limiting Toxicity). The following exception was added to criterion #3: "Grade 3 or 4 asymptomatic increases in amylase or lipase levels for which appropriate evaluation shows no clinical evidence of pancreatitis." This was done to align with the amylase/lipase information in Section 8.3.1 dose modifications.
6. Section 3.1.11 (Evaluability and Subject Replacement) was updated for clarification (changes in bold):

"Phase 1: Subjects in Cohorts 1A through 1C are fully evaluable for DLT if **they fulfill the criteria for the Per-Protocol Population for DLT Assessment. The Per-Protocol (PP) Population for DLT Assessment includes:**

**(1) All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9.** ~~**They experience a DLT, or**~~

(2) ~~**In the absence of a DLT, they**~~ **All subjects with no DLT who** receive at least 75% of the total dose of each study drug and undergo respective safety assessments, without major protocol violations, over the entire DLT evaluation period.

Subjects who are not fully evaluable for DLT will be replaced.

Phase 2: Subjects in Cohort 2 who receive at least 1 dose of each study drug and undergo respective disease assessments, without major protocol violations, are considered fully evaluable and will be included in the Per-Protocol (PP) Analysis Population **for Clinical Efficacy."**

7. Section 3.1.16 (On Study and Post Study Follow-up), 3rd paragraph was clarified (changes in bold): "If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On-Study Follow-up Period (which is 28 days after the last dose of study treatment), any assessments required in the 28 day post-last treatment visit that are not covered as part of the **last** on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the ~~**protocol**~~ **last on-treatment** visit and the 28 day post-last treatment visit should not be repeated."
8. Section 3.2 (Flowchart):
   - Visit name was clarified (changes in bold):

| |
|---|
| ~~**Withdrawal**~~ Visit for Subjects who Discontinue Treatment Prematurely |

   - Hemoglobin A1c was added to screening procedures to align with requirement in Inclusion criteria.
   - Sample collection was deleted for Intratumoral tremelimumab PK. This was to align with removal of Section 4.3 (Tremelimumab PK) from protocol.
   - The following note was added to Footnote 3: ""It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing."
   - The following notes were added to Footnote 5: "See Sections 4.3.1.1 and 5.1 (#2) for details on biopsies" and "Note: the Screening/Baseline biopsy may be done on the Cycle 1/Day 1 Visit as long as it is done prior to start of any treatment."
   - Footnote 8 (regarding tremelimumab PK) was deleted.
   - Footnote 11 was renumbered as #8
   - Collection of blood for all biological markers was added to First On Study Follow-up Visit with newly added Footnote 11, which says "There is no need to repeat these assessments if they were done at the Premature Discontinuation Visit."

9. Section 4.0 (Study Objectives and Endpoints): pharmacokinetics was removed from secondary objectives (see change for Section 4.3, Tremelimumab PK). This was also changed in the Synopsis.
10. Section 4.1.2 (Subject Evaluation and Statistics for Safety): the following clarifications were added (changes in bold): "See Section 3.1.11 for subject evaluability and replacement for DLT assessments **and for description of the Per-Protocol (PP) Population for DLT Assessment**. In addition, all subjects who receive at least 1 dose of tremelimumab, durvalumab, or polyICLC will be assessed for safety and tolerability, regardless of whether or not they are fully evaluable per protocol as defined in Section 3.1.11; **this is the Safety Population.** Appropriate summaries of AEs, **SAEs,** DLTs, laboratory data, and vital sign data will be presented. AEs will be listed individually per subject according to the NCI CTCAE, Version 4.03, and the number of subjects experiencing each AE will be summarized using descriptive statistics."
11. Section 4.3 (Tremelimumab PK) was deleted. Rationale: Systemic levels of tremelimumab after low intratumoral doses are not of interest. Other sections were re-numbered accordingly.
12. Section 5.1 (Inclusion Criteria) #1 was modified based on PI requests for clarification (changes in bold): "Subjects must have histologic confirmation of advanced unresectable disease, have failed at least one standard of care therapy, and do not have curative options. Tumors should be biopsy-accessible (see NOTE 1), measurable cancers of the following histologies:
    - Non-viral-associated head and neck squamous cell carcinoma (HNSCC) or HPV-associated HNSCC after failure of prior therapy
    - Locally recurrent **or metastatic** breast cancer
    - Sarcoma
    - Merkel Cell Carcinoma (MCC)
    - Cutaneous T cell Lymphoma (CTCL)
    - Melanoma after failure of available therapies
    - GU cancers with accessible metastases (e.g., bladder, renal)
    - Any solid tumors with masses that are accessible ~~**without imaging**~~

    NOTE 1: A biopsy-accessible lesion is defined as a tumor lesion which can be, in the opinion of the Investigator or that of consulting physicians, safely accessed for biopsy or for injection by means of physical examination or imaging guided means, **preferably** ~~**such as**~~ ultrasound ~~**or CT scan**~~ (e.g., cutaneous lesions, inguinal nodes, supraclavicular or cervical nodes, superficial abdominal lesions, and lesions that are accessible by ultrasound guidance and not impacting vital organs/structures). NOTE 2: CTCL may respond very differently than solid tumors; therefore, the study will primarily focus on solid tumors, but a "signal-seeking" approach to including some subjects with CTCL will be supported. There will be a limit of < 10-20% CTCL for total enrollment."
13. Section 5.1 (Inclusion Criteria) #2 was changed **FROM:**
    "Subjects with measurable disease as defined by irRECIST and RECIST 1.1: at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded), where each lesion must be ≥ 10 mm when measured by computed tomography (CT), magnetic resonance imaging (MRI), or caliper measurement by clinical examination, or ≥ 20 mm when measured by chest x-ray. To be considered measurable, lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI. Additionally, subjects must have at least 1 measurable lesion of 6 mm diameter by clinical examination or a larger lesion

(approximately 2 cm or more) amenable to multiple core biopsies; multiple small lesions of comparable volume may be biopsied on a single date. Subjects must have at least 2 lesions that can be biopsied or 1 lesion that can be biopsied at least twice."

**TO: "**Subjects need to have at least 2 lesions, as follows:

(1) 1 lesion considered measurable disease as defined by irRECIST and RECIST 1.1, i.e., that can be accurately measured in at least 1 dimension (longest diameter to be recorded), where each lesion must be ≥ 10 mm when measured by computed tomography (CT), magnetic resonance imaging (MRI), or caliper measurement by clinical examination, or ≥ 20 mm when measured by chest x-ray. To be considered measurable, lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI. <u>These lesions should not be injected with study drug or biopsied.</u>

(2) 1 larger lesion (approximately 2 cm or more) amenable to repeated multiple core biopsies or at least 3 smaller lesions of at least 6 mm diameter amenable to repeated single core biopsy, measured by clinical examination. Multiple small lesions of comparable volume may be biopsied on a single date. <u>These lesions must also be suitable for repeated injections of study drug, either as single injection in larger lesions (preferred) or multiple injections in up to 3 smaller lesions.</u>

Ideally, subjects should have at least 1 additional lesion amenable to biopsy. <u>This/these lesion(s) should not be injected with study drug."</u>

<u>Rationale: The criterion was reworded to provide clarification for the lesions that are needed for the study.</u>

14. Section 5.2 (Exclusion Criteria):
    - #1 was modified per PI request (changes in bold): "Prior treatment with combination CTLA-4 and PD-1/PD-L1 blockade, **with the exception of subjects with melanoma."**
    - #7 was updated as follows (changes in bold):
      "Active, suspected or prior documented autoimmune disease (including **but not restricted to** inflammatory bowel disease, celiac disease,~~ **irritable bowel syndrome**~~, Wegner's granulomatosis and Hashimoto's thyroiditis, **etc**.). Participants with vitiligo, **alopecia**, type I diabetes mellitus, residual hypothyroidism **(e.g., following Hashimoto syndrome**) due to autoimmune condition only requiring hormone replacement, psoriasis **or any chronic skin condition** not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. **Subjects without active disease in the last 5 years may be included but only after consultation with the study physician. Subjects with celiac disease controlled by diet alone may also be included**."
      Rationale: irritable bowel syndrome was deleted from the list of examples for autoimmune diseases, as it should not have been included in this category. The remaining changes were clarifications and updates per standard language in current protocols.
    - #17 - contraception language was updated according to current recommendations from MedImmune.
    - #18 was updated for clarification (changes in bold): "Any condition that, in the clinical judgment of the treating physician, is likely **to interfere with the interpretability of the data or** to prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk."

- #19 and #20 were added per current recommendations from Medimmune.

15. Section 5.3.1 (Non permitted Concomitant Therapies): # 2 was updated for clarification (changes in bold): “Other cancer therapy (e.g., drug, radiation, or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1. (6 weeks for nitrosoureas and 12 weeks for antibodies **other than anti-CTLA-4 or anti-PD-1/PD-L1 antibodies**).
16. Section 5.3.2 (Permitted Concomitant Therapies):
    - #6 was clarified as follows (changes in bold): “Hormone or hormone-related anti-cancer therapy, **and cancer supportive therapy such as bone modifying agents (bisphosphonates/RANK-L inhibitors).”**
    - Footnote was corrected (changes in bold): “All prescription and nonprescription drugs must be recorded in the concomitant medications section of the case report form, listing generic (preferably) or brand name, indication, dose, route, and dates of administration. All non-drug therapies must be recorded in the respective sections of the case report form ~~**or as AEs**~~.
17. Section 6 (Study Drug Preparation and Administration): A title header was added to second paragraph: "**Order of Drug Administration.”** A reference was provided to this paragraph in Sections 6.1, 6.2, and 6.3. Also, the following correction was made (changes in bold): “…durvalumab infusion will start **at least** 60 minutes after the end of the tremelimumab infusion.”
18. Section 6.1 (Tremelimumab) and Section 6.2 (Durvalumab): the entire sections were updated and reorganized according to current language for IV infusions from Medimmune / AstraZeneca.
    - Dextrose was added as an option to be used as a diluent for IV bag.
    - Infusion pump requirement was deleted
    - Emphasized that 0.22 or 0.2 µm in-line filter must be used
    - The following statement was added or clarified: “After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.”
    - The following statement was added “See Section 8.3.1 for guidelines for infusion-related reactions.”
    - The following statement was added for each respective section: “Tremelimumab/durvalumab solution should not be infused with other solutions or medications.”
    - Weight restriction for fixed doses of durvalumab was added. Dose calculations/preparation were added or clarified.
    - The following statement was clarified for durvalumab: ”The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new IV bag must be prepared from new vials and the remaining dose is given.”

- The following statement was clarified for IV tremelimumab (changes in bold): "**The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F).** If there are no requirements to slow, interrupt, or permanently stop the infusion, the anticipated infusion time to deliver each dose (250 mL) is anticipated to be 60 (± 5) minutes. **However, if there are interruptions during infusion, the total allowed should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new IV bag must be prepared from new vials and the remaining dose is given.**"
- The following statement was added for tremelimumab: "No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed." The following statement was deleted: "lines containing cellulose based filters should not be used with tremelimumab."
- The following statement was added for tremelimumab: "The IV bag size should be chosen such that the final concentration of tremelimumab after dilution in the bag is between 0.10 mg/mL and 10 mg/mL. The appropriate IV bag size should be chosen for the respective dose. For the 75 mg dose only, tremelimumab may be administered using a 250 mL IV bag."
- The following statement was deleted for tremelimumab only: "An infusion time of less than 55 minutes is considered a deviation.**"**
- The following statement was added for durvalumab: "The IV bag size should be chosen such that the final durvalumab concentration after dilution in the bag must be 1 mg/mL to 15 mg/mL. The appropriate IV bag size should be chosen for the respective dose."
- The removal of a volume of IV diluent equal to the volume of durvalumab or tremelimumab being added to the bag was deleted as it is an unnecessary step as long the defined concentration ranges for the doses in the IV bags are maintained.

19. Section 6.3.1 (PolyICLC Study Drug Information): table was updated to reflect concentration of different lots of PolyICLC (changes in bold):

| | | | |
|---|---|---|---|
| Manufacturer | Oncovir | | |
| Expiration/Retest Date | *Expiration/retest dates are documented on the Certificate of Conformance.* | | |
| Container Description | *Type:*<br>Single-use unpreserved vial | *Material:* | *Size:*<br>1 mL |
| Formulation | PolyICLC is supplied in vials containing 1 mL of ~~**2 mg/mL**~~ opalescent white suspension (**approximately 2 mg/mL**). Each mL of polyICLC for injection contains **approximately** 2 mg/mL poly-IC, 1.5 mg/mL poly-L-lysine, and 5 mg/mL sodium carboxymethylcellulose in 0.9% sodium chloride solution and adjusted to pH 7.6-7.8 with sodium hydroxide. | | |
| Active Ingredient Content | *Mass/Weight:*<br>approximately 2 mg | *Volume:*<br>1 mL | *Concentration:*<br>**approximately** 2 mg/mL |
| Storage Conditions | +2°C to +8°C (approximately 40°F) Do not freeze | | |
| Labeling | Product name, concentration, lot number, date of manufacture, manufacturer, and investigational use statement | | |

20. Section 6.3.3 (PolyICLC Preparation and Administration):
    - The first sentence was updated (changes in bold): "PolyICLC is supplied by the Ludwig Institute for Cancer Research in vials containing 1 mL of ~~**2 mg/mL**~~ opalescent white suspension **(approximately 2 mg/mL)."**
    - The following note was added:

    "NOTE: Lot PJ215-1-10-01 of PolyICLC has a labeled concentration of 2 mg/mL. As the PolyICLC dose is 1 mg, this corresponds to 0.5mL. Lot PJ215-1-10-01 expired on 28 FEB 2018 and was replaced by Lot PJ215B03. Lot PJ215B03 has a concentration of 1.8 mg/mL. For a 1 mg dose using this lot, the volume to be administered is 0.556 mL (this number may be rounded according to institutional practice). The volume administered for subsequent lots should be adjusted accordingly so that the administered dose is 1 mg."
    - In the subsequent paragraphs for PolyICLC, reference to these directions was provided for volume required.
21. Section 6.5 (Monitoring of Tremelimumab and Durvalumab IV Dose Administration). The following note was added for clarification: "Note: When IV durvalumab and IV tremelimumab are to be administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even though vital signs assessment is not required during the entire 60-minute period post tremelimumab."
22. Section 7.1.6 (Expedited Serious Adverse Event Reporting Requirements). The following statement was added: "Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement."
23. Section 7.1.8 (AESIs). The section was updated and reorganized based on updated recommendations from Medimmune in the updated IB. Specifically:
    - Additional information was added to the description of the AESIs
    - Myocarditis, myositis/polymyositis, other inflammatory responses, and hypersensitivity and infusion reactions were added.
    - The following sentence was added "Guidelines for the management of subjects experiencing toxicities for PolyICLC can be found in Section 8.4."
24. Section 8.3.1 (Durvalumab and Tremelimumab Dose Modification Due to Toxicity): Immune-related AEs were updated based on updated Toxicity Mgt Guidelines from Medimmune (Dated 01Nov2017). Specifically, myocarditis, myositis/polymyositis were added; Diarrhea/colitis, elevated creatinine, rash, and endocrinopathies were updated.
25. Section 8.3.2 (Durvalumab and Tremelimumab Dose Modification Not Due to Treatment-related Toxicities): Section was changed

    **FROM:** Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply: 1. If the subject misses 2 consecutive planned doses, the subject should be discontinued from treatment; 2. If the dosing interruption is ≤ half the planned dosing interval, the originally planned drug administration should be given. Any respective protocol deviation should be documented, if applicable; 3. If the dosing interruption is greater than half the planned dosing interval, the dosing should be skipped, and the next scheduled drug administration should be performed. The respective protocol deviation should be documented.

    **TO:** Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative

reasons, whereby the following rules should apply: 1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days. All resulting protocol deviations should be documented; 2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued; 3. If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the timing of the next dose(s) should be adjusted in accordance with #1, if necessary; 4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary.

26. Administrative Changes:
    - "IT" was changed to "intratumoral" throughout the document to provide clarification. ITM was used in the tables due to space constraints.
    - Spelling, grammar and typographical errors were corrected.
    - Formatting/administrative changes were implemented, as applicable.
    - Updated List of abbreviations

**Amendment 5**
**Issue date: 13-MAY-2019**
**Summary of Changes:**

1. Section 3.1.10 (Subject Withdrawal from Treatment or from Study). The following note was changed (changes in bold). Rationale: For this study, irRECIST is the primary method for determining response and progression rather than RECIST 1.1.

"NOTE: Subjects meeting criteria for radiographic progression by ~~**RECIST 1.1**~~ **irRECIST** (Section 8.5) will be allowed to continue on therapy until confirmation of progression **by irRECIST** if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
b. No significant decline in ECOG performance status;
c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention."

2. In accordance with the change in Section 3.1.10, the following change from RECIST 1.1 to irRECIST was made to Section 3.2 (Flowchart – footnote 8) and Section 4.2.1 (Clinical Efficacy-Endpoints and Assessment Methods). In addition, the change in time period ("4 to 6 weeks" to "4 to 8 weeks" was done to align with the visits in the study. (Changes in bold.)
"Subsequent imaging at 4 to ~~**6**~~ **8** weeks after first documentation of ~~**RECIST 1.1**~~ **irRECIST**-defined progression must be performed."
3. Section 3.1.11 (Evaluability and Subject Replacement). The PP definition for subjects in Phase 2 was clarified to provide better guidance for minimum drug requirements (changes in bold):

"Phase 2: Subjects in Cohort 2 ~~**who receive at least 1 dose of each study drug and undergo respective disease assessments, without major protocol violations,**~~ are considered fully evaluable and will be included in the Per-Protocol (PP) Analysis Population for Clinical Efficacy **if they meet the following criteria:**

- **Receive at least the following minimum quantities of study drugs over the subject's entire treatment period:**

- **2 durvalumab administrations**
- **3 tremelimumab administrations**
- **10 polyICLC administrations (regardless of route)**

- **Undergo appropriate disease assessments (radiological or clinical)**
- **Have no major protocol violations that would have an effect on the efficacy evaluation.**

**Subjects who are not fully evaluable for PP population for Clinical Efficacy may be replaced."**

4. Section 5.2 (Exclusion Criteria) #4 was changed to provide clarification regarding the intention of the criterion regarding brain metastases (change in bold):
"Subjects with history or evidence upon physical examination of central nervous system (CNS) disease, including primary brain tumor, seizures not controlled with standard medical therapy, any **active** brain metastases, or, within 6 months of the first date of treatment on this study, history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage."
5. Formatting/administrative changes were implemented, as applicable.
6. Section 6.1.1 (Tremelimumab study drug information). The following was added:

Tremelimumab is also available in a 25 mg/vial format; the concentration remains 20 mg/mL.

| | | | |
|---|---|---|---|
| Manufacturer | MedImmune | | |
| Expiration/Retest Date | *Expiration/retest dates are documented on the QA Disposition of Investigational Medicinal Product (IMP) Report.* | | |
| Container Description | *Type:* Single-use vial | *Material:* Clear glass | *Size:* 2 mL |
| Formulation | Liquid solution containing 25 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5. | | |
| Active Ingredient Content | *Mass/Weight:* 25 mg/vial | *Volume:* 1.25 mL/vial | *Concentration:* 20 mg/mL |
| Storage Conditions | +2°C to +8°C (36°F to 46°F). Do not freeze. Allowable Short Term Temperature Variation: 2°C to 25°C for 7 days | | |
| Labeling | Product name, lot number, and storage conditions | | |

**Amendment 5.1**
**Issue date: 23-JUL-2019**
**Summary of Changes:**

1. Section 6.1.1 (Tremelimumab study drug information) The highlighted line was deleted from the 25 mg/vial table. The deleted information was inadvertently included in Amendment 5.

| | |
|---|---|
| Storage Conditions | +2°C to +8°C (36°F to 46°F). Do not freeze. ~~Allowable Short Term Temperature Variation: 2°C to 25°C for 7 days~~ |

**2.** Section 5.3.1 (Non-permitted concomitant therapies). Criterion # 5 was clarified as follows (changes in bold): "Drugs with laxative properties and herbal or natural remedies for constipation should **generally** be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea, **but, for example, opiate-induced constipation may be treated with laxatives at the Investigator's discretion."**

**Amendment 6.0**
**Issue date: 02-NOV-2021**
**Summary of Changes:**

1. All subjects have completed treatment, and by the date of implementation of this amendment, all subjects will have completed On Study Follow-up. This amendment provides that the Post Study Follow-up for the collection of survival data will be discontinued as of 28 February 2022, and the study will be completed. (This note was added to the synopsis.)
   a. The following note was added to Sections 3.1.15.2 (Duration of Study), 3.1.16 (On Study and Post Study Follow-up), and 4.2.1.3 (Overall Survival): "NOTE: Per Amendment 6.0, all post study follow-up for the collection of survival data will be discontinued as of 28 February 2022 (see rationale in Section 8.1, Amendment 6.0 on Page 80)."
   b. Section 3.2 (Study Flowchart): Footnote 12 was added, "Per Amendment 6.0, all post study follow-up for the collection of survival data will be discontinued as of 28Feb2022 (see Section 8.1, Amendment 6.0)."
2. AstraZeneca provided updated language for Section 7.1.2 (Additional expedited reporting requirements for this study). Section 7.1.2.4 (New Cancers) and Section 7.1.2.5 (Deaths) were added.
3. Section 7.1.6 (Expedited SAE Reporting Requirements): updated address for Drug safety Contact and Primary Sponsor Contact due to office move.

   Ludwig·Institute·for·Cancer·Research↵
   ~~666~~·600·3rd·Ave·~~28th~~·Floor·32¶
   New·York,·New·York·~~10017~~10016↵
4. Administrative edits: In Section 7.1.6, the title of Primary Sponsor Contact was changed from Director to Senior Director.

## 8.2 Participating Study Sites, Investigators and Staff, Laboratories, and Sponsor Information

This information is maintained in the Clinical Study File.

## 8.3 Dose Adjustments and Delays for Durvalumab and Tremelimumab

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline (i.e., the guideline that provides for the greatest dose reduction, dose delays or holds) should be followed.

### 8.3.1 Durvalumab and Tremelimumab Dose Modifications due to Toxicity

Durvalumab (MEDI4736) and tremelimumab administration may be modified or discontinued as a result of toxicities as described in the table below.

Additional information and guidance regarding dose modification due to toxicity are provided from Medimmune in the following guideline:

> Medimmune's 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).

Dose modifications will not be required for AEs that are clearly not attributed to durvalumab or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

| **MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity** |
|---|
| **Note: If M and T dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next <u>scheduled</u> treatment date.** |
| ***<u>Immune-related Adverse Events (irAEs)</u>***<br>Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Maximum supportive care, including immunosuppressive medications, such as high dose steroids, is allowed to induce resolution of the event. **However, infliximab should not be used for management of immune-related hepatitis.**<br>In addition to the criteria for permanent discontinuation of M and T depicted below, **<u>permanently discontinue M and T</u>** also for:<br>• Any Grade rash with bullous skin formations.<br>• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen.<br>• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.<br>• **Any Grade biopsy-proven immune-mediated myocarditis.**<br>**Grade 1**<br>• In general, no dose modification required.<br>• For *pneumonitis/interstitial lung disease and myocarditis*, consider holding M and T dosing as clinically appropriate and during diagnostic work-up for other etiologies. |

**Grade 2**

- In general, hold M and T until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue M and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of M and T may differ by event as detailed below.
- For *myositis/polymyositis*, hold M and T until resolution to ≤ Grade 1; permanently discontinue M and T if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.
- For *pneumonitis/interstitial lung disease and myocarditis*, the decision to reinitiate M and T upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria).
- For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue M and T permanently if there are signs of respiratory insufficiency or autonomic instability.
- For *endocrinopathies, other than isolated hypothyroidism and isolated Type 1 diabetes mellitus*, follow general instructions above, but patients may be retreated if the endocrinopathy is controlled and the patient is clinically stable while requiring steroid doses of ≤ 10 mg/day prednisone equivalent.
- For *isolated hypothyroidism* managed with hormone replacement therapy, *isolated Type 1 diabetes mellitus* treated with appropriate diabetic therapy, and for *sensory neuropathy/neuropathic pain*, holding M and T is at the discretion of the Investigator.
- For *elevated creatinine* or *rash*, M and T should be held until resolution to ≤ Grade 1 or baseline and after completion of steroid taper
- For *vitiligo*, no dose modification required.

**Grade 3**

- In general, hold M and T until resolution to ≤ Grade 1, and after the end of any steroid taper, and discontinue M and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of M and T may differ by event as detailed below.
- For *myositis/polymyositis*, follow Grade 2 instructions above.
- For *peripheral neuromotor syndromes (*such as *Guillain-Barre* and *Myasthenia Gravis),* apply respective Grade 2 rules.
- For *endocrinopathies*, follow Grade 2 instructions above.
- For *diarrhea/colitis*, permanently discontinue M and T if toxicity does not improve to ≤ Grade 1 within 14 days.
- For *pneumonitis/interstitial lung disease, myocarditis, and elevated serum creatinine (e.g., nephritis or renal dysfunction)*, always discontinue M and T permanently.
- For *asymptomatic increases of amylase or lipase* levels, hold M and T, and if complete work up shows no evidence of pancreatitis, M and T may be continued.
- For *hepatitis*, discontinue M and T permanently for (1) transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days, (2) transaminases > 8 × the upper limit of normal (ULN) or bilirubin > 5 × ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury").
- For *rash*, M and T should be held until resolution to ≤ Grade 1 or baseline.

| MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity |
|---|
| **Grade 4**<br>• In general, discontinue M and T permanently.<br>• For *endocrinopathies,* follow Grade 2 instructions above.<br>• For *asymptomatic increases of amylase or lipase* levels, hold M and T, and if complete work up shows no evidence of pancreatitis, M and T may be continued. |
| ***Infusion-related Reactions***<br>**Grade 1**<br>• The infusion rate of M and T may be decreased 50% or temporarily interrupted until resolution of the event.<br>• Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the Investigator.<br>• Premedication for subsequent doses should be considered.<br>• Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions<br>**Grade 2:**<br>• **Same as Grade 1**, but consider giving subsequent infusions at 50% of the initial infusion rate.<br>**Grade 3 and 4:**<br>• **The infusion must be stopped i**mmediately and treatment permanently discontinued.<br>• Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid). |
| ***All other Adverse Events***<br>**Grade 1**<br>• No dose modification required.<br>**Grade 2**<br>• Hold M and T until resolution to ≤ Grade 1 or baseline, and discontinue M and T permanently if such resolution does not occur within 60 days.<br>**Grade 3**<br>• Hold M and T. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume M and T administration at next scheduled dose. Otherwise, discontinue M and T permanently.<br>**Grade 4**<br>• In general, discontinue M and T permanently.<br>• For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment in consultation with the Sponsor. |

### 8.3.2 Durvalumab and Tremelimumab Dose Modification Not Due to Toxicities

Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply:

1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two IV doses of durvalumab or tremelimumab shall be no less than 21 days. All resulting protocol deviations should be documented.
2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
3. If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the timing of the next dose(s) should be adjusted in accordance with #1, if necessary.
4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary.

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## 8.4 PolyICLC Toxicity Management, Dose Delays and Adjustments

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline (i.e., the guideline that provides for the greatest dose reduction, dose delays or holds) should be followed.

### 8.4.1 Management of Injection Site Reactions

**Intratumoral Injection**

Some degree of inflammatory response in the injected lesion is expected as part of the therapy. Prior to each intratumoral injection, the maximal diameter of peritumoral inflammation will be recorded in millimeters and photographically, if appropriate in the judgment of the investigator, as a baseline for subsequent post-injection measurements.

Pain medication to be administered includes, if needed, acetaminophen, diphenhydramine, benzodiazepines, and/or opiates. Other analgesics may be given at the discretion of the investigator.

**IM administration**

PolyICLC IM injections are usually well tolerated, with few issues (general fatigue and malaise).

### 8.4.2 Management of Systemic Toxicities

The most common systemic drug-related AEs—Grade 1 or 2 chills, flu-like symptoms and fever—typically resolve in < 48 hours and do not require dose reductions or a delay in the dosing regimen.

**Anti-emetics**

Prophylactic anti-emetics will be administered at the discretion of the study physician.

**Anti-inflammatory and Pain Medication**

Corticosteroids and other immunosuppressant drugs should not be used to control polyICLC-associated AEs unless indicated in the opinion of the study physician and sponsor.

Acetaminophen will be used to treat fever or flu-like side effects of polyICLC. Subjects may be pretreated with acetaminophen as warranted by previous side effects, at the discretion of the local investigator. NSAIDS may be given if necessary at the discretion of the study physician.

### 8.4.3 PolyICLC Dose Modifications due to Toxicities

PolyICLC will be dosed as defined in Section 3.1.7. Delays or skipped doses of polyICLC should not delay or shift the timing of other treatment agents.

In the event that steroids are administered to treat tremelimumab or durvalumab irAEs, dosing of polyICLC should be withheld during the time period that steroid administration is given.

## 8.5 RECIST 1.1 and irRECIST Guidelines

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were revised in 2009 as RECIST 1.1.(55) These guidelines have been the widely accepted criteria to assess response and progression in solid tumors; however, limitations have been noted in the use of RECIST 1.1 for immunotherapy trials. With immunotherapeutic agents, clinical trials have shown that complete response, partial response, or stable disease status can still be achieved after an initial increase in overall tumor burden, and regression of initial lesions may occur despite development of new lesions. The Immune-related Response Criteria (irRC) were developed to address the need for response criteria in an immunotherapy setting.(56) The main difference with irRC was that it considered the subject's total tumor burden at each subsequent assessment and required confirmation of suspected disease progression with subsequent imaging, approximately four weeks later. In addition, a greater number of lesions (10 vs. 5) were measured in a bidimensional manner instead of unidimensionally as in RECIST 1.1. In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.(57) Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).(58) The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines. The guidelines for RECIST 1.1 are summarized below, followed by a summary for irRECIST.

### RECIST 1.1

The following section outlines the RECIST 1.1 guidelines as published (55) and as summarized by National Cancer Institute for CTEP-involved clinical trials**.**

**I. Disease Parameters for RECIST 1.1**

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

**NOTE for irRECIST: During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.**

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness

recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

**NOTE for irRECIST: Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.**
**Brain lesions detected on brain scans can be considered as both target or non-target lesions depending on the protocol definition.**

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

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

## II. Methods for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological

response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.(59-61) In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.(62)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

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

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

## III. Response Criteria for RECIST 1.1

### A. Evaluation of Target Lesions

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

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

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

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

**B. Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

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

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

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

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

**C. Evaluation of Best Overall Response**

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

**2. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)**

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

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

**D. Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

## irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. (58) are presented below.

### I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1. One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease

### II Follow-up Assessments in irRECIST

#### *A. Follow-up recording of target and new measurable lesions*

**A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.**

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

#### *B. Follow-up non-target assessment*

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

#### *C. Follow-up for New Non-Measurable Lesions*

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

### III Overall Assessments for irRECIST

**The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions**.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

| **Overall Assessments by irRECIST** | |
|---|---|
| **Complete Response (irCR)** | Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. |
| **Partial Response (irPR)** | Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions<br>• If new measurable lesions appear in subjects with **no target lesions at baseline**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation<br>• irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response.<br>• Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints. |
| **Stable Disease (irSD)** | Failure to meet criteria for irCR or irPR in the absence of irPD |
| **Progressive Disease (irPD)** | Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.<br>• In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression.<br>• IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening |
| **Other** | **irNE:** used in exceptional cases where insufficient data exist.<br>**irND:** in adjuvant setting when no disease is detected<br>**irNN:**, no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD |

## 8.6 Exploratory Assessment of Correlative Immunologic Research

Please refer to the laboratory manual for additional instructions and information on specimen handling and logistics.

### 8.6.1 Effects on the Tumor Microenvironment

Tumor biopsies will be obtained at Baseline (pretreatment), Day 15, and, provided there is sufficient tumor to biopsy, at Day 29 (Cycle 2, Day 1), and optionally at the time of progression and at the end of treatment.

Endpoints include induction of a favorable immune signature and increased T-cell infiltration, as well as pre-treatment and post-treatment immune signatures that predict clinical response.

### 8.6.2 Circulating Soluble Factors

Blood samples will be collected for analyses of circulating soluble factors as outlined in Section 3.2. This includes cytokines, chemokines, and antibodies. The timing of the collection of these samples will match the timing of collection of tumor biopsy samples so that the effects in the blood and tumor can be correlated.

### 8.6.3 Peripheral blood mononuclear cells (PBMC)

Samples will be collected for analyses at the time points designated in the study flowchart (Section 3.2).

Peripheral blood populations before and after treatment will be assessed numerically and functionally by flow cytometry and other assays (e.g., ELIspot). Measures will include immune cell phenotypes, numbers of immune cells (T cells, T cell subsets, NK cells, B cells, myeloid derived suppressor cells), Immune cell activation and function, Immune diversity, and functional cellular immune responses. These will be assessed by flow cytometry to evaluate the association with treatment and subject responses.

### 8.6.4 RNA Profiling

Samples will be collected for analyses at the time points designated in the study flowchart (Section 3.2).

## 8.7 ECOG Performance Status

**ECOG Performance Status:** Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair. *

| GRADE | ECOG PERFORMANCE STATUS |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 5 | Dead |

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

## 8.8 List of Abbreviations

| | |
|---|---|
| ADA | anti-drug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration time curve |
| CD | Cluster of differentiation |
| Cmax | peak concentration |
| CRF | Case report form |
| CTC | Circulating tumor cell |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | Cytotoxic T lymphocyte-associated antigen 4 |
| DC | Dendritic cell |
| DLT | dose-limiting toxicity |
| ECLA | Electrochemiluminescence assay |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed paraffin-embedded |
| FTIH | First time in human |
| GCP | Good Clinical Practice |
| GMP | Good manufacturing practice |
| HLA | Human Leukocyte Antigen |
| HNSCC | Head and neck squamous cell carcinoma |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IGSF | Immunoglobulin superfamily |
| IHC | Immunohistochemistry |
| IL | interleukin |
| IMiD | Immune modulatory drug |
| IND | Investigational new drug |
| irAE | Immune-related adverse event |
| irRC | immune-related response criteria |
| irRECIST | Immune-related Response Evaluation Criteria In Solid Tumors |
| IM | Intramuscular |

| | |
|---|---|
| ITM | intratumoral |
| IV | intravenous |
| IRB | Institutional Review Board |
| LICR | Ludwig Institute for Cancer Research |
| M | MEDI4736 (durvalumab) |
| mAb | Monoclonal antibody |
| MDSC | myeloid derived suppressor cells |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MSD | Meso Scale Discovery |
| MTD | maximum tolerated dose |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NSCLC | Non-small cell lung cancer |
| NK | Natural killer |
| ORR | Objective Response Rate |
| OS | Overall survival |
| PBMC | Peripheral blood mononuclear cell |
| PD-1 | Programmed death-1 |
| PD-L1 | Programmed death ligand 1 |
| PFS | Progression free survival |
| PK | Pharmacokinetics |
| PolyIC | Polyinosinic-polycytidylic acid |
| PolyICLC | polyIC stabilized with polylysine and carboxymethylcellulose as polyICLC (Hiltonol®, Oncovir Inc.). |
| Q4W | Every 4 weeks |
| RCD | Recommended combination dose |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| T | Tremelimumab |
| TME | Tumor microenvironment |
| TIL | tumor-infiltrating lymphocyte |
| TLR | Toll like receptor |
| ULN | Upper limit of normal |
| WFI | Water for Injection |

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