Memorial Sloan Kettering Cancer Center
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A Phase 2 Trial of TPIV200/huFR-1 (a multi-epitope anti-folate receptor vaccine) Plus anti-PD-L1 Antibody durvalumab (MEDI4736) in Patients with Platinum Resistant Ovarian Cancer

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

A Phase 2 Trial of TPIV200/huFR-1 (a multi-epitope anti-folate receptor vaccine) Plus anti-PD-L1 Antibody durvalumab (MEDI4736) in Patients with Platinum Resistant Ovarian Cancer

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This is a prospective, non-randomized, phase 2 study which will assess the efficacy and safety of a combination vaccine and immune checkpoint inhibitor for platinum resistant adnexal (ovarian, fallopian tube, and primary peritoneal) cancer (generally referred to as Ovarian Cancer). Forty women with persistent or recurrent high grade epithelial adnexal carcinomas, who have had at least one prior platinum chemotherapy regimen and have progressed within 6 months of their most recent dose of platinum will be eligible for treatment if they have measurable disease and adequate organ function. Patients with clinically significant autoimmune disease will be excluded. Treatment cycles will be 28 days and will continue until toxicity or disease progression, for up to 12 cycles.

Primary Objective

- Determine the effectiveness of the combination by measuring Overall Response Rate [ORR = Complete Response (CR) + Partial Response (PR)] by RECIST and Progression Free Survival (PFS) rate at 6 months

Secondary Objectives

- Disease Control Rate (DCR = CR+PR + stable disease [SD] ≥ 12 weeks)
- Progression Free Survival (PFS)
- Safety of the combination assessed by observed Adverse Events (AE's) and immune-related AE's (irAE's). A stopping rule will be employed for excess toxicity.
- Response rate as evaluated by irRECIST criteria
- Measure expression of Folate Receptor-alpha (FRα) and PD-L1 on primary tumors.
- Assess the ability of the combination to elicit an immune response.
- Correlate FRα-specific immune responses and PD-L1 expression with clinical efficacy.

Patient Population

- Sample size: 40 patients
- Patients with persistent or recurrent high grade adnexal (ovarian, fallopian tube, or primary peritoneal) carcinoma, whose disease has progressed within 6 months of completing a prior platinum regimen
- Adequate organ function and performance status ECOG 0-1
- At least 1 target lesion, which is measurable by RECIST and was not previously irradiated

Treatment Plan:

Patients will receive an intradermal (ID) injection of TPIV200 (500 µg per peptide) and GM-CSF (125 µg per peptide) on Day 1 of cycles 1-6. They will also receive intravenous (IV) injections of durvalumab (750mg) on Days 1 and 15 of cycles 1-12. Radiologic tumor assessment will be repeated every 12 weeks (or 3 cycles) during and after treatment, until time of progression. Treatment will continue until progression, intolerance, withdrawal, study

completion, or study termination. It is estimated that full accrual will be achieved within 18 months; 2.5 years is estimated between time of opening and time of last treatment.

	Cycles 1-6	**Cycles 7-12**
40 Patients Platinum-Resistant Ovarian Cancer	Days 1,15: durvalumab (750mg IV over 60 min)	Days 1,15: durvalumab (750mg IV over 60 min)
	Day 1: TPIV + GMCSF (500µg/peptide+125µg ID)	

*1 Cycle = 28 Days; Tumor Assessment Q3 Cycles; Biomarkers Baseline and EOS.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Endpoints

- Overall tumor Response Rate (CR+PR) and will be assessed by RECIST 1.1. Pre-defined deviations from RECIST will be permitted to allow select patients deemed to be benefitting from treatment to receive continued therapy.

- Co-primary endpoint supplementary to ORR: Progression Free Survival (PFS) rate at 6 months.

Secondary Endpoints

- Assess the safety of delivering the doublet, by determining rate of irAE, SAE, therapy completion rate, and protocol completion. A stopping rule will halt the study if excess toxicity is encountered.
- Disease Control Rate (CR+PR+SD)
- Estimate median PFS
- Response rate as evaluated by irRECIST criteria
- Estimate median Overall Survival (OS).
- Determine the ability of the laboratory parameters to predict response:
    - Tumor tissue FRα expression*
    - Tumor tissue PD-L1 expression**
    - Tumor tissue immune-related gene signature
    - Peripheral blood immune phenotype
    - Peripheral blood gene expression profiling
    - Peripheral blood cellular and serologic responses to FRα
    - Peripheral blood T cell receptor repertoire

* FRα levels (using a Morphotek, Inc. FRA-26B3 IHC Assay Kit) will be performed by TapImmune; PD-L1 staining expression (Ventana SP263 assay kit) will be performed by AZ/MEDI.

**Immune response monitoring will be performed at MSK.

3.0 BACKGROUND AND RATIONALE

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Introduction

Immunotherapy with checkpoint inhibition is improving long-term disease control for patients with diverse malignancies (Tolapian 2012; Hamid 2013; Wolchok 2013; Powles 2014), including patients with ovarian cancer (OC) (Hodi 2008; Brahmer 2012). The primary mediators of adaptive immune blockade, whose targeting in clinical trials have yielded results, include CTLA-4 (Hodi 2010; Ribas 2013), PD-1 (Topalian 2012; Hamid 2013; Robert 2014), and PD-L1 (Brahmer 2012). Responses in tumors such as melanoma, non-small cell lung cancer, and renal cell cancer have been impressive. Preclinical data point toward an important role of TIL's in OC. (Zhang 2003; Sato 2005; Hamanishi 2007) Emerging human data in OC demonstrate more modest yet encouraging activity of immune checkpoint inhibitors (Hodi 2008; Brahmer 2012).

Checkpoint Inhibition in OC

Programmed cell death ligand 1 (PD-L1) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir et al, 2008; Park et al, 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen, 2008).

In one preclinical study, the 5-year survival rate in OC patients with low expression of PD-L1 was 80.2% compared with 52.6% in patients with high expression levels of PD-L1 (Hamanishi et al. 2007). In a Phase 2 study of 20 heavily-pretreated patients with platinum resistant OC, nivolumab (anti-PD-1) at 2 dose levels yielded an ORR of 15%; and a 45% disease control rate; responses were durable for 2 disease assessments beyond the end of treatment in the 2 patients with CR (Hamanishi 2015). On the heels of these results, a randomized CTEP trial of nivolumab alone or in combination with ipilimumab for OC has been initiated.

Durvalumab: anti-PD-L1 Monoclonal Antibody

Durvalumab, formerly called MEDI4736, is a human mAb of the IgG1κ subclass that inhibits binding of PD-L1 to PD-1 and CD80. Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Antibodies of the IgG1 isotype have the potential to trigger effector functions such as ADCC and CDC. However, durvalumab carries 3 point mutations in its constant domain that reduce binding to C1q as well as the affinity of the Fc domain for the ADCC-inducing Fcγ receptors (Oganesyan et al, 2008).

Preclinical analyses reveal the following features:

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 and CD80
- *In vitro*, durvalumab can relieve PD-L1-mediated suppression of human T-cell activation
- Durvalumab does not trigger ADCC or CDC in cell-based functional assays
- Durvalumab inhibits tumor growth in a xenograft model via a T-cell dependent mechanism
- An anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy

To date, several hundred patients with a range of solid tumors have been treated on integrated monotherapy studies with durvalumab. These trials (CD-ON-MEDI4736-1108, D4190C00002, and D4190C00007) have yielded information on clinical safety, efficacy, and PK, as summarized below. (Investigator's Brochure, durvalumab (MEDI4736), vol. 8.0)

Pharmacokinetics

Study CD-ON-MEDI4736-1108: As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (Cmax) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

As of 09Feb2015, a total of 388 subjects provided samples for anti-drug antibody (ADA) analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

Safety

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

(anti-CTLA-4) combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

Study CD-ON-MEDI4736-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%).

Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-MEDI4736-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis

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(3 subjects) and increased GGT (2 subjects). There were no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Efficacy

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007).

Study CD-ON-MEDI4736-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

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

Fixed Dosing

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

Similar findings have been reported by others [Ng et al 2006, Wang et al. 2009, Zhang et al, 2012,Narwal et al 2013]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [3]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [Zhang et al 2012].

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

FRα and the FRα Vaccine TPIV200

One reason that responses in OC appear to be less robust than for other solid tumors may be its relatively low mutational burden (TCGA 2011). The success of immune checkpoint inhibition may partly relate to the breadth of the mutational landscape (Rizvi 2015), with melanoma and NSCLC having the highest mutation loads among solid tumors, providing a feast of immunologic targets. Mutational load and neoantigen landscape may be predictive of response to CTLA-4 inhibitors in patients with melanoma (Snyder 2014).

An important question in OC is whether the efficacy of checkpoint inhibition can be improved by enhancing immunologic targets. Only a few tumor-associated antigens (TAAs) have been identified in OC. One notable example is the folate receptor alpha (FRα), which presents an compelling opportunity for targeted immunotherapy. The human FRα is over-expressed in a majority of ovarian cancers (70-90%), but is rarely found in healthy adult tissues. While it is a self antigen, several promiscuous epitopes of FRα have been identified to prompt a T cell response in 70% of patients with ovarian and breast cancers (Knutson 2006).

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Based on these observations, a multi-epitope anti-FRα vaccine (huFR-1 or TPIV200 – TapImmune, Inc.) was developed by identifying the five most highly antigenic moieties of FRα identified in a group of un-vaccinated patients with OC and breast cancer, as compared with normal volunteers. Using these 5 oligopeptide antigens, TPIV200 was designed, generated, and validated in animal models, and subsequently tested in human subjects (Investigators Brochure, TPIV200, TapImmune, Inc.).

In a phase 1 study, 22 women in remission from OC or breast cancer were vaccinated with TPIV200 admixed GM-CSF in a single syringe. (Proc ASCO 2015) One cycle of cyclophosphamide was given in an effort to reduce T-regs. The safety profile of TPIV200 was excellent. Immune responses were measured, using IFN-γ ELIspot assays in the 21 patients who had adequate numbers of specimens. Robust increases in FRα specific T cell immune responses were detected in all evaluable patients. All 5 of the constituent peptides were found to be immunogenic and all patients appeared to have developed immune responses to at least 2 and, in the majority, more than 3 of the vaccine peptides. Vaccination with peptide also led to generation of T cells that recognize naturally processed antigen from the FRα protein. Clinical efficacy could not be evaluated, since all patients were in clinical remission. T-regs were not measurably reduced.

While many attempts to target FRα in OC have not yielded benefits, the validity of FRα as a therapeutic target for OC has been bolstered by the impressive clinical activity of mirvetuximab soravtansine (IMGN853), in recurrent OC in a phase 1 trial reported at ASCO 2015. IMGN853 is an antibody-mytansoid conjugate, which is FRα-specific (Ab 2015; Moore 2015). Levels of FRα measured by immunohistochemistry correlated with response. Although FRα can be detected in small amounts in healthy adult lung and kidney, pulmonary toxicities were rare and renal toxicity was not observed.

Furthermore no significant pulmonary or renal toxicity was encountered in studies using farletuzumab (Konner 2010), an anti-FRα MAb, shown to induce ADCC in preclinical models, despite radiolabeling studies confirming tumor-targeting (Smith-Jones 2008); nor was such toxicity seen in clinical trials with vintafolide, a folate-vinca conjugate, also demonstrated to home to tumors by radio-imaging SPECT studies (Naumann 2013).

Hypothesis

In clinical trials, peptide vaccines have demonstrated measurable immunogenicity in OC patients vaccinated against the FRα as well as other TAA's. Vaccines alone however have yet to demonstrate compelling evidence of clinical efficacy (Tse 2014). For this study, we hypothesize that the therapeutic potential of anti-cancer vaccines is hindered by immune checkpoints in the suppressive tumor microenvironment, and furthermore that immune checkpoint inhibition may overcome these restraints. In the proposed study, patients with platinum resistant OC will be vaccinated with TPIV200 and given concurrent durvalumab. It is expected that these agents will be tolerable at full doses of each, given their mild, and non-overlapping toxicity profiles. Safety and efficacy will be evaluated. Immunologic assays will be utilized to characterize the specific cellular and humoral immune responses generated

against vaccinated peptides and other potential TAA's to evaluate for evidence of epitope spreading.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an MSKCC investigator-initiated, single-center, non-randomized, open-label, phase 2 study to evaluate the activity of TPIV200 + durvalumab in patients with recurrent or persistent platinum resistant OC. The safety and tolerability of this doublet will also be evaluated.

Each cycle will be 28 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination.

Efficacy assessments will be performed every 3 cycles (or 12 weeks) from initiation of study treatment until disease progression is documented.

Safety will be evaluated through the monitoring of all serious and non-serious AEs and irAE's, graded according to the current version of National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v. 4.03). A safety stopping rule will be used to terminate the study early if excess toxicity is encountered.

4.2 Intervention

Eligible patients will undergo screening and baseline procedures per the Study Schedule. Study inclusion and exclusion criteria will be applied per section 6.0. Enrolled patients will receive durvalumab IV (intravenous Sec on Days 1 and 15) during Cycles 1-12 and TPIV200+GM-CSF ID (3 intradermal injections on Day 1) during Cycles 1-6. Each cycle will be 28 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination.

Efficacy assessments will be performed at the initiation of study treatment and then every 3 cycles (or 12 weeks) until radiologic and/or clinical disease progression. Patients who discontinue treatment for reasons other than progression may continue efficacy assessments until progression is demonstrated. Patients who demonstrate radiologic progression by RECIST criteria may be considered for continued therapy (but not primary efficacy analysis) if they are deemed to be clinically benefiting, according to predetermined permitted criteria (section 12.4). Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs and irAEs, graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC v.4.03).

The order of administration on Days 1 of Cycles 1-6 is durvalumab followed by TPIV200. Durvalumab (750mg) will be infused IV over 1 hour on Days 1 and 15 of Cycles 1-12. On Cycle 1 Day 1, TPIV200 should be administered as soon as possible after the 60 (+/-5) min post-infusion vital sign check. For subsequent doses, post-infusion vitals are not required (unless patient has experienced hypersensitivity to durvalumab), and TPIV200 should be administered as soon as possible after the end of durvalumab infusion.

TPIV200 (500µg per peptide) will be admixed with 125µg granulocyte-macrophage colony stimulating factor (GM-CSF) [adjuvant] and injected ID on Day 1 of Cycles 1-6. The peptide/GM-CSF mixture will be injected at 3 sites ID, preferably on the forearm.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 FRα peptide vaccine with adjuvant (GM-CSF)

5.1.1 FRα peptide vaccine

Background: The tumor antigen targeted by the vaccine is folate receptor alpha (FRα), a high affinity folate-binding protein that is overexpressed on 70-90% of ovarian tumors. The vaccine contains five peptides: FR30, FR56, FR76, FR113, and FR238 [Investigator Brochure, TapImmune, Inc.].

Formulation: The vaccine including the 5 peptides formulated together will be provided as a single lyophilized glass vial. Each vial will contain 0.550 mg of each of the 5 peptides for a total of 2.75 mg. The peptide and formulation are GMP quality.

Storage: Vaccine vials should be stored at -20ºC at controlled temperature.

Refer to the FRα vaccine (TapImmune, Inc.) investigator brochure for detailed information about the vaccine.

5.1.2 Sargramostim (Leukine®, GM-CSF)

Background: Sargramostim stimulates proliferation, differentiation and functional activity of neutrophils, eosinophils, monocytes, and macrophages.

Formulation: Commercially available

Injection, powder for reconstitution: 250 µg [contains mannitol 40 mg/mL and sucrose 10 mg/mL]

Liquid injection: 500 µg/mL [contains mannitol, tromethamine, benzyl alcohol]

Preparation, storage, and stability: Store intact vials under refrigeration at 2ºC to 8ºC (36ºF to 46ºF), do not freeze. Do not shake. Sargramostim powder for injection may be reconstituted with 0.5mL preservative free Sterile Water for Injection (SWFI) or bacteriostatic water for injection (with benzyl alcohol 0.9%) for a final concentration of 500 µg /mL. Preparations made with SWFI should be administered as soon as possible, and discarded within 6 hours of reconstitution. Preparations made with bacteriostatic water may be stored for up to 20 days at 2ºC to 8ºC. Gently swirl to reconstitute; do not shake.

Refer to the manufacturer's labeling information for Leukine®.

5.1.3 Preparation of vaccine for ID injections:

The ID syringes for injection of the FRα peptide vaccine with adjuvant (GM-CSF) will be prepared prior to each injection by a site pharmacist according to the instructions below (preparation). The pharmacist will then have the syringes delivered to bedside for injection as soon as practical but no more than 6 hours after preparation.

Preparation of the FRα peptide vaccine with adjuvant (GM-CSF)

Thaw peptide vials in the refrigerator or at room temperature for 1 to 2 hours. Bring vaccine to room temperature, before preparing the dose. When reconstituting, mix the solution in the vial by gentle swirling; do not shake.

Do not refreeze vaccine peptides after thawing

- Remove a vial of GM-CSF from the refrigerator and allow to reach room temperature.
- Add 0.5 mL of water for injection to reconstitute lyophilized GM-CSF to a concentration of 500 µg/mL. If liquid product is used, there is no need to reconstitute; the concentration is 500 µg/mL.
- Add 1.1 mL of water for injection to reconstitute lyophilized peptide vial.
- Mix vial as needed to resolubilize the peptides.
- Allow the vial to sit upright for a minute.
- Withdraw 0.275 mL of GM-CSF and add to the peptide vial containing 2.75 mg of peptide. Swirl to mix.
- Load THREE tuberculin syringes with ~0.41 mL of the peptide/GM-CSF mixture.

Labeling and delivery of syringes

Label each syringe with:

- Patient ID
- Time of preparation (HH:MM)

Have the labeling confirmed by a second pharmacist

Deliver the 3 syringes immediately for injection to the patient.

5.2 Durvalumab

The Pharmaceutical Development R & D Supply Chain Management section of AstraZeneca/MedImmune will supply durvalumab (MEDI4736) to the investigator as a concentrate for solution for infusion.

Formulation/packaging/storage

Durvalumab is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial). The solution will be diluted with 0.9% (w/v) saline for IV infusion.

Unopened vials of liquid durvalumab must be stored at 2°C to 8°C (36°F to 46°F). Durvalumab must be used within the individually assigned expiry date on the label.

In use storage and stability

Total in-use storage time from needle puncture of durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Durvalumab does not contain preservatives and any unused portion must be discarded.

Study drug preparation

Calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose of 750mg.

Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.

An additional volume of 0.9% (w/v) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab.

The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific subjects and should not be shared between subjects.

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

Dose administration

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein or central access device.

Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection) or dextrose, is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

Monitoring of dose administration

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment (Section 8.0).

In the event of a Grade ≤ 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50%, or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade ≥ 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Subjects must have recurrent or persistent platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with measureable disease (as defined by RECIST 1.1.) who have received at least one prior platinum-based therapy.

   Platinum-based therapy is defined as treatment with carboplatin, cisplatin or another organoplatinum compound.

   Platinum-resistant is defined as having had disease progression within 6 months or most recent platinum therapy, or having disease progression while receiving previous platinum-based chemotherapy.

Histologic documentation of diagnosis of carcinoma is required and the following histologic subtypes are eligible: high grade serous, clear cell, endometrioid, carcinoma, adenocarcinoma, mixed (including above subtypes only).

2. Age ≥ 18 years

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

4. Resolution of (non-laboratory) adverse effects of recent surgery, radiotherapy, or chemotherapy to Grade ≤1 prior to first study treatment (with the exception of alopecia or neuropathy; chemotherapy-induced peripheral neuropathy up to Grade ≤2 will be permitted).

5. Patients must have measurable disease. Measurable disease is defined by RECIST (version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) and has not been previously irradiated. Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

6. Adequate normal organ and marrow function defined by the following laboratory results obtained within 14 days prior to first treatment:

   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm^3)
   - Platelet ≥ 100 x 10^9/L (>100,000 per mm^3)
   - Hemoglobin ≥ 9.0 g/dL
   - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). (Unless Gilbert's Syndrome, without concurrent clinically significant liver disease)
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
   - Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

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

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

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

6.2 Subject Exclusion Criteria

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

2. Participation in another clinical study with receipt of an investigational product during the last 4 weeks

3. Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab

4. History of another primary malignancy except for:

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

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

   - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)

   - Adequately treated stage 1 breast or stage 1 low grade endometrial cancer.

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

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

7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Steroid pre-medication for CT scan contrast or study drug, is allowable, regardless of dose.

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

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

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

11. History of primary immunodeficiency

12. History of allogeneic organ transplant

13. History of hypersensitivity to durvalumab or any excipient

14. History of hypersensitivity to TPIV200

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

16. Known history of previous clinical diagnosis of tuberculosis

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

18. Subjects who are pregnant, breast-feeding or of reproductive potential who are not employing an effective method of birth control

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

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

21. Subjects with uncontrolled seizures.

22. Known hypersensitivity reaction to the GM-CSF adjuvant

23. Patients who have developed any evidence of clinical or radiologic pneumonitis, COP/BOOP, or other lung injury, during treatment with prior FRα-targeting therapy, such as mirvetuximab soravtansine (IMGN853), or with any prior cancer immunotherapy.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator or research team within the Gynecologic Medical Oncology Group at Memorial Sloan Kettering Cancer Center (MSKCC). Patient recruitment will occur in the Gynecologic Medical Oncology clinics at MSKCC. The investigator will discuss the study with suitable participants, and should the patient consent to proceed with protocol therapy, will enroll their patients in the research study. Approximately 2-4 patients will accrue onto this study per month. All participants will be women.

8.0 PRETREATMENT EVALUATION

Within 28 days prior to treatment start:

- Written informed consent/assignment of subject identification number
- History and Physical examination with Adverse event/serious adverse event assessment
- Review of concomitant medications
- Vital signs (blood pressure, heart rate and temperature), weight and height
- Performance status

- Toxicity assessment
- Radiographic tumor measurements (CT C/A/P, MRI, Chest X-ray)
- Request archival tumor (10-20 PPFE slides or tissue block).

Within 14 days prior to treatment start:

- Complete Blood Count (CBC) with differential and platelets
- Comprehensive profile (BUN, creatinine (or creatinine clearance), sodium, potassium, chloride, CO2, calcium, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- Thyroid function tests (TSH and fT3 and fT4)[g]
- Coagulation tests: prothrombin time, APTT and INR (PT/PTT)
- Magnesium
- LDH
- Amylase
- Lipase
- Uric Acid
- CA125
- Gamma GTP
- Body weight
- Urinalysis
- Pregnancy test (in women of child bearing potential)
- 12 lead ECG (in triplicate)
- Research bloods

Single tracing ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion for Cycle 1 Day 1 and Cycle 5 Day 1. The screening ECG may be used in place of pre-infusion Cycle 1 Day 1 ECG, if it was performed within 14 days prior.

ECGs recorded during the screening period will be obtained in triplicate (with 2-5 minute lag time between each); ECGs recorded during the treatment phase will be single tracing. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 10.0. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. On Cycle 5 Day 1, ECGs will be recorded within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On durvalumab treatment days, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses (at dose levels of 10 mg/kg or less), the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

The following clinical laboratory tests will be performed (see the Schedule of Assessments, Section 10.0 for the time points of each test):

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

Table 1. Hematology Laboratory Tests

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

Table 2. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium

Table 2. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyl transferase[b]	Uric acid

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

Table 3. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

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

9.0 TREATMENT/INTERVENTION PLAN

Forty patients may be treated. An initial safety lead-in (described in detail under Safety Analysis in Section 14.0) will require that at least 4 patients are observed for at least 4 weeks. The first 3 patients must be staggered by 3 weeks. No more than 3 patients will be enrolled during each 3 week period thereafter.

All subjects will receive TPIV200+GM-CSF and durvalumab. Each cycle will be 28 days in duration. The order of administration on Days 1 of Cycles 1-6 is durvalumab followed by TPIV200. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination.

Durvalumab (750mg) will be infused intravenously (IV) over 1 hour on Days 1 and 15 of Cycles 1-12.

TPIV200 (500µg per peptide) will be admixed with 125µg Granulocyte-macrophage colony stimulating factor (GM-CSF) and injected intradermally (ID) on Day 1 of Cycles 1-6. The peptide/GM-CSF mixture will be injected into at least 3 sites ID, preferably on the forearm. For patients with a history of breast cancer who have not had lymph node dissections on one side, the forearm on the side without node dissections will be used unless the patient prefers to use the upper outer leg. For patients with prior bilateral lymph node dissection, a site on the outer upper leg should be used.

Efficacy assessments will be performed every 3 cycles from initiation of study treatment until disease progression. Patients who discontinue treatment for reasons other than progression may continue efficacy assessments until progression.

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs and irAEs, graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events. A stopping rule will be applied to halt the study if excess toxicity is encountered.

Pre- and post-treatment blood and serum samples, as well as archival tumor tissue (when available) will be collected for biomarker analysis (as per Appendix D).

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All assessments to be performed pre-infusion unless stated otherwise. A Cycle is 28 Days.

Parameter	**Screening**		**Cycle 1**		**Cycles 2-6**		**Cycles 7-12**		**End of Treatment**	**Follow-up**
Day	**28 days before[a]**	**14 days before**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**		
Consent	x									
Medical History	X									
Concomitant Medications	X		x	x	x	x	x	x	x	
Request Archival tumor tissue	X									
Physical Examination	X		x		x		x			
ECOG	X									
Weight	X		x		x		x			
Vital Signs (BP, HR, and temperature), height	X		x	x	x	x	x	x		
Adverse Event Assessment	X		x	x	x	x	x	x	x	
CBC		X	x		x		x		x	
Comp		x	x	X	x	X	x		x	
TSH		x	x	X	x	X	x		x	
Free T3 & Free T4[b]		x	x	X	x	X	x			
PT/PTT		x	As clinically indicated							
CA-125		x	Every 6 weeks for the first 6 cycles				As clinically indicated			
GGT		x	x	As clinically indicated						
Amylase, LDH, Lipase, Uric Acid, Magnesium		x	x	x	x	x	x		x	
HIV [G]	X									
Hepatitis [H]	X									
Urinalysis		x			x		x			

Pregnancy Test		X	As clinically indicated							
Research bloods [c]		X	X	X	X	X				
12- Lead ECG [d]		X	X	Cycle 5 Day 1						
Durvalumab			X	X	X	X	X	X		
TPIV200			X		X					
Radiographic disease assessment [e]	X		Every 3 cycles (or 12 weeks)							Every 12 weeks
Follow-up call or visit [f]										X

[a] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Cycle 1 Day 1. A +/- 3 Day window is allowed for all scheduled treatments and associated parameters, unless otherwise specified.
[b] Draw free T3 and free T4 only if TSH is abnormal, beginning no later than first subsequent draw. May discontinue if TSH normal on 2 consecutive blood draws.
[c] Research bloods will consist of 4 CPT tubes, and will be drawn at 4 time points. The baseline draw may be on Cycle 1 Day 1, or up to 14 days prior. The on-treatment research bloods may be drawn on Cycle 1 Day 15, Cycle 2 Day 15, and Cycle 3 Day 1 (C1D15, C2D15, and C3D1), or up to 7 days prior. For all of these blood draws, the tubes must be transported to the Immunotherapy Core Lab at ZRC (Zuckerman Research Center) by 5 PM on the same day.
[d] ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion. For Cycle 1 Day 1, the screening ECG may be used in place of pre-infusion ECG, if it was performed within 14 days prior. ECGs recorded during the screening period will be obtained in triplicate (with 2-5 minute lag time between each); ECGs recorded during the treatment phase will be single tracing.
[e] Radiographic disease assessment have a +/- 7 day window. Patients who are off study and have not progressed/withdrawn consent will have scans done every 12 weeks until POD
[f] A follow-up call or visit will be done 90 days (+/- 2 weeks) after the last treatment.
[G] If unknown
[H] Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody

11.0 TOXICITIES/SIDE EFFECTS

The dose delay instructions provided in this section are intended to serve as guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while ensuring patient safety. Patients may temporarily suspend dosing of study drug for up to 14 days if they experience toxicity that is considered related to study drug and requires that a dose be held. Patients who miss ≥ 28 consecutive days of scheduled study treatment because of drug-related AEs will be discontinued from the study. Exceptions may be made after discussion with and approval by the Principal Investigator.

Patients may suspend dosing of study drug for radiation therapy or surgery that is considered by the treating physicians to be of clinical benefit for the patient. After completion of the intervention, patients may restart the study drug as long as all criteria for dosing are met and there is no evidence of disease progression (unless approved by PI and sponsor as noted previously).

11.1 Durvalumab

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (see below).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- In addition, there are certain circumstances in which durvalumab should be permanently discontinued.
- Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (see **APPENDIX A**). Dose reductions are not permitted.
- Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.
- Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Tables 1, 2, and 3, respectively.
- In addition, management guidelines for adverse events of special interest (AESI's) are detailed in Section 11.4.1.3. All toxicities will be graded according to NCI CTCAE v4.03.

Contraception

Females of childbearing potential who are sexually active with a nonsterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product, or for at least 90 days following the last infusion of durvalumab or until after 4-5X the half-life of durvalumab or until the time specified in the prescribing information of durvalumab, whichever occurs longest; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Subjects must use 2 acceptable methods of effective contraception as described in Table 5.
- Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 5) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Effective methods of contraception (two methods must be used)

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

[a] This is also considered a hormonal method.

Permitted concomitant medications

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

Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

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

Table 4. Prohibited and Rescue Medications

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

11.2 TPIV200+GM-CSF

Deviations from schedule: Deviations are permitted with the following windows: 3 day forward or backward during vaccinations 1-6. If a deviation is allowed, the patient should plan to return to the original vaccination schedule with the next visit.

Dose reduction or delay is not permitted. Patient will be followed if study treatment is discontinued for toxicity. Study treatment should be discontinued for unacceptable toxicity, defined by:

- Grade 3 allergic reaction, or higher with the exception of fever. (Grade 2 allergic reaction is defined as rash, flushing, urticaria, or dyspnea; Grade 3 allergic reaction is defined as symptomatic bronchospasm, requiring parenteral medication, with or without urticaria, allergy related edema or angioedema; Grade 4 allergic reaction is defined as anaphylaxis.)
- Grade 2 or higher autoimmune reaction (Grade 2 is defined as evidence of autoimmune reaction involving a non-essential organ or function (e.g. hypothyroidism) requiring treatment other than immunosuppressive drugs. Grade 3 is a reversible autoimmune reaction involving a major organ (e.g. colitis)
- ≥ Grade 3 hematologic or non-hematologic toxicity including fever. (Grade 3 fever is > 40ºC for < 24 hours).
- Grade 3 injection site reaction. (Grade 3 is defined as ulceration or necrosis that is severe or prolonged, or requiring surgery).

11.3 General

The toxicity profiles of the different investigational agents are generally non-overlapping. Emergence of novel toxicities resulting from the combination is not expected, but patients will be carefully monitored for unexpected events.

It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (≥ 24 hours) Grade ≥3 toxicity in spite of optimal medical management require delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. Dose delay for durvalumab will follow the toxicity management algorithm Tables found in Appendix A.

Other non-hematologic toxicities with an impact on organ function of Grade ≥2 require delay in subsequent therapy for a maximum of 28 days until recovered to Grade 1, or pre-therapy baseline.

Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, romiplostim and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

11.4 Assessment of Safety

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

Safety Parameters

11.4.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

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

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

11.4.2 Definition of Serious Adverse Events (SAE's)

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

- Results in death
- Is immediately life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

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

11.4.3 Definition of Adverse Events of Special Interest

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

AESIs for durvalumab 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 etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with durvalumab include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis

- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)

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

Pneumonitis

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

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Section 6.6.1.

11.4.4 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

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

11.4.5 Hepatic function abnormalities (hepatotoxicity)

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

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

investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Appendix A.

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2x ULN may need to be reported as SAE's, 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.

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

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

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

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

Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc)

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix A.

11.4.6 Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [22]. 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 criteria.

12.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm 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 will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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.

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 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.

12.3 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 followup. 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), but NOT lung.

CA125: CA125 alone cannot be used to assess response. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

12.4 Response Criteria

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.

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 CA125 is initially above the upper normal limit, it 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 CA125 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).

Evaluation of Best Overall Response

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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.

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.

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 endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

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.

Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of recurrence, progression, or death, whichever occurs first.

Survival

Survival is defined as the duration of time from start of treatment to time of death or the date of last contact

Permitted Deviations from RECIST

The study's efficacy objectives will be evaluated according to the standard, unmodified RECIST v1.1 criteria described in section 12.3, and that, within the context of this protocol, the only purpose of the modifications to the criteria is to allow certain patients to continue the study treatment despite meeting RECIST criteria for progression of disease.

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

- Response to immunotherapy may be delayed

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

As long as they are receiving treatment on protocol, patients will be permitted to continue study treatment after RECIST v 1.1 criteria for POD are met if they meet all of the following criteria:

- Absence of symptoms and signs indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial apparent progression

Patients in whom radiographic disease progression is confirmed at the subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of clinical benefit.

Modification of RECIST as described may discourage the early discontinuation of durvalumab + TPIV200 and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST v 1.1 criteria.

Patients who have permanently discontinued study treatment must discontinue study participation if they experience disease progression per RECIST v 1.1.

The primary reason for study treatment discontinuation should be documented on the eCRF.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab + TPIV200 or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor, spinal cord compression).

irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. (48) 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.

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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 (TA), 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 • 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 • 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. • 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. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • 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. **irND:** in adjuvant setting when no disease is detected **irNN:**, no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

12.5 Biomarker Assessment

The study will include analyses of archival tumor tissue and peripheral blood to define the biomarkers that could predict/correlate with response. Research bloods will be collected pre-treatment at 4 pre-specified time points: Day 1, Day 15 (C1D15), Day 43 (C2D15) , and Day 85 (C3D1) with a window of -14 Days for the Day 1 Draw and -7 Days for every subsequent draw. Four CPT tubes will be collected at each time point. CPT tubes will be supplied to participating Regional and Alliance sites. Once the CPT tubes are drawn, the tubes will be couriered at room temperature to Immune Monitoring Core facility at ZRC (Zuckerman Research Center, 415 East 68th St., Room 1513). If this is not feasible, patients may have the CPT draws performed at 53rd street or any other participating site within specified windows.

12.5.1 Tissue FRα expression (TapImmune)

Archival tissue slides will be shipped to the sponsor (TapImmune) to assess the levels of FRa expression by IHC.

12.5.2 Tissue PD-L1 expression (AstraZeneca/MEDImmune)

Archival tissue slides will be shipped to the sponsor (Astra Zeneca/MEDImmune) to assess the levels of PD-L1 expression in tumor cells and tumor-infiltrating immune cells.

12.5.3 Tissue gene expression profiling and IHC (MSKCC, Zamarin, Wolchok lab)

By using Nanostring nCounter PanCancer Immune Profiling Panel, and immunofluorescence microscopy, archival tumor tissue will be assessed for tumor infiltration with various immune cell subsets, including CD8 cells, CD4+ effector cells (FoxP3-), CD4+ regulatory T cells (FoxP3+), and myeloid cells (CD68+). Tumors will also be assessed for the expression of the known activating co-stimulatory receptors such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS, as well as known immune inhibitory components such as PD-L1, indoleamine dioxygenase (IDO), B7-H3, B7-H4, LAG3, TIM-3, PD-1, CTLA-4, VISTA, and BTLA. The expression of each gene will be treated as a continuous variable. For exploratory biomarker analyses, patients will be dichotomized on the basis of the primary efficacy endpoint.

12.5.4 PBMC immunophenotyping (MSKCC: IMF)

By using multi-parameter flow cytometry, we will explore whether peripheral blood biomarkers could serve as early predictors of clinical benefit and provide targets for further combinations, with a particular focus on targetable markers of T cell activation (ICOS, CD137, OX40, GITR), and inhibition (LAG3, TIM3, PD-1, BTLA, VISTA), as well as percentages of peripheral inhibitory immune subsets such as MDSCs and Tregs.

12.5.5 PBMC gene expression analyses

RNA extracted from PBMCs collected at baseline and on-treatment will be analyzed on the Nanostring platform using Nanostring nCounter PanCancer Immune Profiling Panel, to define gene signatures associated with clinical benefit.

12.5.6 PBMC vaccine-specific immune responses (MSKCC: IMF)

Whole blood will be collected at baseline and at 4 and 8 weeks post-therapy initiation. CD8 and CD4 cells will be analyzed for development of FRa-specific T cell responses by restimulation with FRa peptide and intracellular cytokine staining.

12.5.7 PBMC T cell receptor (TCR) repertoire analyses (MSKCC: IMF, Zamarin, Wolchok lab)

DNA isolated from PBMC's will be send for deep sequencing of TCR CDR regions at Adaptive Biotechnologies to determine whether maintenance or emergence of particular oligoclonal populations of T cells in the periphery is predictive of clinical benefit.

12.5.8 Serologic assays (MSKCC, Fleisher, Thoren).

Sera collected at baseline and at 4 and 8 weeks post-therapy will be analyzed for development of serologic responses to FRa. Using Surface Plasmon Resonance, these antibodies will be characterized for titers, isotype, and affinity to FRa, These measures will be correlated to clinical outcomes.

12.5.9 Identify HLA class I-binding peptides from FRα that are recognized by patient lymphocytes prior to and after therapy. Assess which out of the 5 peptides correlates with the number of lymphocytes prior to and after therapy.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Any patient who withdraws will be encouraged to return to the study center for a treatment completion visit. Patients who discontinue early should return within 30 days following the final dose of study treatment. The primary reason for discontinuation must be recorded in the medical record.

Patients may be withdrawn from the study if they experience any of the following:

- Disease progression, per investigator assessment
- Intolerable toxicity of study drugs

Other reasons for patient discontinuation may include, but are not limited to, the following:

- Change in patient eligibility
- Non-compliance
- Patient decision
- If the patient becomes pregnant
- If treatment is delayed for more than 28 consecutive days

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, visits); or if the investigator determines it is in the best interest of the patient.

14.0 BIOSTATISTICS

This study aims to assess the activity of durvalumab + TPIV200 in patients with recurrent or persistent ovarian or fallopian tube or primary peritoneal cancer.

Prior monotherapy studies of immune checkpoint inhibitors in ovarian cancer have yielded overall response rates in the range of 10-15%, and may serve as a basis for historical comparison of the doublet tested here.

Study	N	ORR (CR+PR)	DCR (ORR+SD)	Prior Therapy
Nivolumab (anti-PD-1)		15% (3/20):		≥ 2 priors
1 mg/kg q 2 weeks (cohort 1)	10	10% (1 PR)	50% (5 SD +1 PR)	Platinum Resistant
3 mg/kg q 2 weeks (cohort 2)	10	20% (2 CR)	40% (2 SD +2 CR)	
Avelumab (anti-PD-L1)				med 4 priors (1-11)
Phase Ib expansion cohort				Platinum Resistant
10 mg/kg q 2 weeks	75	10.7% (8 PR)	55% (33 SD +8 PR)	
Pembrolizumab (anti-PD-1)				>80% ≥ 4 priors
Phase Ib expansion cohort				
10 mg/kg q 2 weeks	26	11.5% (1 CR, 2 PR)	35% (9 SD+1CR+2 PR)	PD-L1+ (IHC)

ORR (defined as CR+PR) will be the primary endpoint. A 10% ORR will be considered low and 25% or higher will be considered promising for further studies. Forty patients provide 90% power and Type I error of 10% using a Simon two stage design. There will be an interim analysis after 27 patients and if 3 or more responders (CR+PR) are observed out of 27

patients then the study will continue to the second stage. At the end of the study we require 7 or more responders out of 40 patients to declare this study positive and the agent worthy for further investigation.

Unacceptable response rate: 0.1
Desirable response rate: 0.25
Error rates: Type I = 0.1 ; Type II = 0.1

# responses required in Stage I	# patients accrued at stage I	# responses required in Stage I	Total sample size
>=3	27	>=7	40

If the test for ORR is significant, then the PFS rate at 6 months will also be tested against the historical control estimate. For PFS rate at 6 months, we consider a 15% rate as low, and a rate of 35% or higher as indicative of promising activity. This test of PFS rate will be performed only if the ORR analysis is significant, and thus PFS assessment is supplementary to ORR assessment. At the end of the study, if 10 or more out of 40 patients are considered progression free at 6 months, then the combination will be considered worthy of further study. This study will have 94% power and 7% Type I error to show activity in terms of 6 months PFS rate. The overall Type I error of the study is bounded by the 10% error rate of the first hypothesis of ORR. The hierarchy in the two hypotheses for ORR and PFS ensures the overall error rate to be smaller than 10% (Bretz 2009)

Based on historical accrual rates in similar populations, we anticipate successful enrollment of 3-4 patients per month yielding a total accrual time of 18 months. Accrual will continue until 40 (evaluable patients are defined in section 12.1), unless the interim analysis after 27 patients does not support continuation.

Efficacy Variables
The intent of this protocol is to assess the vaccine-checkpoint inhibitor combination for activity in patients with recurrent platinum-resistant epithelial adnexal carcinomas. There are no treatment comparisons involved. For the purpose of this study 'platinum resistance' will refer to patients who have exhibited progressive disease (clinical, radiologic, or serologic) within 6 months of completing a previous course of platinum therapy (primary, secondary, or other).

The principal parameters employed to evaluate the efficacy of the combination are:

- The rate of ORR and duration of overall objective response (ORR = CR + PR).
- The frequency and severity of observed adverse effects.
- Progression-free survival rate at 6 months for all patients evaluable for this endpoint.

Patients who have have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for response and PFS. The primary efficacy analysis will include only patients who are evaluable for response. Patients without post baseline assessment of response will be included in a sensitivity analysis as non responders for ORR, and events for PFS. For safety, all patients who received at least one cycle of therapy will be included.

Definitions of Statistics to be Reported

- Disease Control Rate (DCR), defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) ≥12 weeks from the start of treatment will be reported and the 90% confidence interval will be estimated using exact binomial proportions. This will be done following RECIST criteria.
- Progression free survival (PFS), defined as the duration of time from start of treatment to time of recurrence, progression, or death due to any cause, whichever occurs first. Patients will be censored at last follow up date. The Kaplan Meier estimate of median PFS will be reported as well as the PFS rate at 6 months
- Overall survival (OS), defined as the duration of time from start of treatment until the date of death due to any cause. Patients will be censored at last follow up date. The Kaplan Meier estimate of median OS will be reported.
- Duration of response (DOR), defined as the time from which measurement criteria are met for CR or PR (whichever status is recorded first using RECIST) until the first date of documented disease progression, will be estimated using the Kaplan Meier method. Patients without documented progression will be censored at last follow up.
- The rate of response using immune response criteria (refer to irRECIST description in section 12.3, which defines responders and non responders) and the 90% confidence interval will be estimated using exact binomial proportions.
- Adverse events by the current version of Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03) will be tabulated in order to assess the safety profile and tolerability therapy in treated patients.

Safety Analysis

A stopping rule will be incorporated into this single stage design in order to address safety.

The rates of irAE, SAE, therapy completion rate, and protocol completion will also be reported.

Safety will be measured by the frequency of grade 3 or 4 treatment-related clinically significant toxicities (NCI Common Terminology Criteria for Adverse Events version 3.0), aside from Grade 3 or 4 hematologic or laboratory abnormalities, unless they are deemed unexpected or clinically significant. We assume that a 20% rate of clinically significant treatment-related adverse event, such as persistent or unexpected renal injury or pulmonary toxicity, or clinically significant laboratory abnormality, is an unacceptable toxicity rate. The trial will be terminated at any point if at least 7 out of 40 patients experience a grade 3/4 protocol-related adverse event that is unique to the combination. Using this stopping rule, the probability of stopping the trial early for various hypothetical toxicity rates is as follows:

True toxicity rate	10%	15%	20%	25%	30%
Probability of early stopping	10%	40%	71%	90%	98%

Frequencies of toxicities will be tabulated. The grade 3 or 4 treatment-related non-hematologic/non-laboratory toxicity will be estimated at the end of the trial along with the 95% confidence interval. With 40 patients, these rates can be estimated within ±16%.

In addition to the Stopping Rule described above, a four-week safety monitoring period will begin once 4-6 patients begin treatment. No subsequent patients may receive protocol therapy until the 4th treated patient completes 4 weeks on study. If any of the first 4 treated patients is invaluable for toxicity through week 4, the monitoring period will extend to the 5th patient, etc, for a maximum of 6 patients. Once at least 4 patients have been observed for at least 4 weeks, treatment of subsequent enrollees may

then resume at the discretion of the Principle Investigator. Observance of 1 or more unexpected, clinically-significant SAE that is possibly, probably, or definitely related to protocol therapy should prompt consideration to amend or terminate the protocol.

Methods of Efficacy Analysis

Efficacy measures such as Overall Response rate (ORR) and PFS rate at 6 months and median progression free survival (PFS) will be estimated. Clinical Benefit Rate (CBR) will be defined as ORR + Stable Disease (SD) rate.

As per the standard of reference set by the Gynecologic Oncology Group for platinum resistant ovarian cancer, if a new agent has a true response rate of 10% or less, it would be considered of little clinical significance. Conversely, if the true response rate is at least 25%, further investigation is clearly indicated. These are the reference ORR numbers used to assess novel agents in the GOG-0126 queue, through which nearly 40 treatments have been evaluated. As a means of comparison, and to further justify this ORR goal, the clinical data for several relevant cytotoxic and biologic agents are tabulated here.

Rx	ORR (%) [PR + CR]	CB/DCR (%) [ORR + SD]	PFS (m)	Response Duration (m)	# of Patients (n)	Reference
Topotecan	6.5		3.1		124	Gordon, JCO 2001
Liposomal Dox	12.5		2.1		130	Gordon, JCO 2001
Gemcitabine	17	54		4.8	17	D'Agostino, Gyn Onc 2002
Docetaxel	22				22	Rose, Gyn Onc 2003
Weekly Paclitaxel	21	67		3.6	21	Markman, Gyn Onc 2006
Nivolumab	15		3.5		20	Hamanishi, ASCO 2015
Pembrolizumab	11.5	35		>6.2-8.3	26	Varga, ASCO 2015
Avelumab	10.7	55			75	Disis, ASCO 2015
Bev	16		4.4		36	Cannistra, JCO 2007
Chemo[a]	12		3.4	2.1-2.8	182	Pujade, JCO 2014
Chemo + Bev	27		6.7	4.2-5.5	179	Pujade, JCO 2014
Olaparib[b]	31	73		7.4	193	Kaufman, JCO 2015
IMGN853	13-22[c]	61			23	Borghaei, ASCO 2015

CB/DCR = Clinical Benefit or Disease Control Rate

[a]The chemotherapy dosing regimens used in the AURELIA trial were as follows:

- Paclitaxel 80 mg/m^2 IV on days 1, 8, 15, and 22 every 4 weeks
- Pegylated liposomal doxorubicin 40 mg/m^2 IV on day 1 every 4 weeks
- Topotecan 4 mg/m^2 IV on days 1, 8, and 15, every 4 weeks or 1.25 mg/m^2 on days 1 to 5 every 3 weeks

[b]All patients had germline deleterious mutations in BRCA 1/2.
[c]An additional 7/23 patients (30%) had a decrease in CA-125 marker.

Given the inherent difficulty in detecting meaningful overall survival (OS) data in patients who will likely frequently receive multiple, and divergent downstream agents after end of study, including possible enrollment in additional clinical trials, PFS is considered an appropriate endpoint for meaningful clinical efficacy. (Broglio 2009) This approach has been adopted for ovarian cancer. (Bast 2007; Markman 2007)

Secondary objectives:

- Determine the ability of the laboratory parameters to predict response:

- Tumor tissue FRα expression*
- Tumor tissue PD-L1 expression**
- Tumor tissue immune-related gene signature
- Peripheral blood immune phenotype
- Peripheral blood gene expression
- Peripheral blood cellular and serologic responses to FRα
- Peripheral blood T cell receptor repertoire

- For exploratory biomarker analyses, patients will be dichotomized on the basis of clinical benefit (CB) rate (CR+PR+SD) as the outcome measure. All biomarkers will be treated as continuous variables and minimum p value approach will be used to define the appropriate cutoffs. For tissue based biomarkers, CBR will be correlated to the level of tissue expression of FRa, PD-L1, or specific genes/gene signatures identified from transcriptional profiling. Levels of gene expression and their relationship to CB will be assessed graphically in order to explore potential cutoffs for expression that related to CB. For peripheral blood biomarkers, changes in specific biomarkers (e.g. change in ICOS level expression on lymphocytes) from baseline levels will be assessed graphically in order to explore potential cutoffs for expression that related to CB.
- Identify HLA class I-binding peptides from FRα that are recognized by patient lymphocytes prior to and after therapy. Assess which out of the 5 peptides correlates with the number of lymphocytes prior to and after therapy. This aim is exploratory and hypothesis generating.
- Determine whether the elicitation of FRα-specific immune responses correlated with clinical efficacy. Binary variables such as +/- MDSC's, or +/- FR-specific T Cells measured at **weeks 2, 6,** and 12 will be assessed with PFS in a Cox model taking into account the time-dependent nature of these biomarkers obtained during treatment. Depending on the number of events, the sample size might limit definitive conclusions and this analysis is exploratory.
- Analyze whether FRα-specific antibodies elicited by protocol therapy can be detected by surface plasmon resonance (Dr. Thoren, Fleischer laboratory)

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or

verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

NA

16.0 DATA MANAGEMENT ISSUES

A research study assistant (RSA) will be assigned to study. The responsibilities of the RSA include project compliance, data collection, extraction and data entry, data reporting, coordination of the activities of the protocol study team and, and of the flow of regulatory paperwork.

The data collected for the study will be entered into a secure database (CRDB). All routine blood test results required per the protocol will be captured in CRDB in addition to baseline medical conditions and disease information, response assessments, off-study documentation, and toxicity grade and attribution. Source documentation will be available to support the computerized patient record.

MSKCC will hold the IND and will be responsible for all safety monitoring. All SAEs will be reported to the MSKCC IRB. The safety of the study will be monitored by the MSKCC Data and Safety Monitoring Committee.

Weekly registration reports will be generated by the RSA and reviewed by the PI to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies.

Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study. Recurrent lapses in data collection, deviations or violations will be discussed with the study team and a corrective plan will be generated. Accrual goals and factors impacting accrual goals will be discussed at the weekly New Patient/Protocol meetings.

If accrual proceeds more quickly than anticipated, it may be slowed or staggered at the discretion of the Principal Investigator, to account for safety concerns or data management resources.

16.1 Quality Assurance

The data and safety monitoring plan at Memorial Sloan Kettering Cancer Center was approved by the National Cancer Institute in September 2001. The plan addressed the new policies set forth by the NCI and the document entitled "Policy of the National Cancer Institute for data and safety monitoring of clinical trials" which can be found at http://grants.nih.gov/grants/guide/noticefiles/not98-084.html. The DSM plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC data and safety monitoring plan can be found on the MSKCC Internet at http://inside2/clinresearch/Documents/MSKCC Data and Safety Monitoring Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. Memorial Sloan Kettering Cancer Center has set up three distinct monitoring processes for our clinical trials program. There are two sub-committees that have the responsibility of data and safety monitoring. These are joint sub-committees with dual-reporting responsibilities. The Data and Safety Monitoring Committee (DSMC) is the sub-committee responsible for monitoring all Phase 1, 2, 1/2, pilot and non-phase clinical trials. The Data and Safety Monitoring Board (DSMB) is the sub-committee responsible for monitoring Phase 3 randomized clinical trials. The Therapeutic Response Review Committee (TRRC) is the sub-committee of Research Council responsible for the independent therapeutic response review for participants in IRB/PB approved clinical trials where therapeutic efficacy is a stated primary objective, typically phase 2 and 3 trials. Formal monitoring of such studies is designed to ensure that the interests of the participants are being scrutinized on a regular basis, and that the trial is progressing in a satisfactory manner.

The DSMC convenes once per quarter and monitors the risk participants are exposed to, the progress of the study, the adequacy of the data storage and whether sufficient data are being entered into the CRDB. The DSMC monitors phase 1, 2, 1/2, pilot and non-phase trials that are not being monitored by an industrial sponsor, and which meet the NCI definition of a Clinical Trial. This trial will qualify for monitoring by the DSMC.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required, and the monitoring procedures will be established at the time of protocol activation. A detailed description of the data to be collected, process of data collection (i.e., data manager and/or data management office), database that will be utilized for data collection and storage (e.g., Clinical Research Database (CRDB), user-supported software), reporting requirements of the data to the institution (IRB), the sponsor and/or governing agency.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 90-days after the participant's last investigational treatment or intervention. Any events that occur after the 90-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSK)

- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

Ethical conduct of the study

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

17.2.1 Recording of adverse events and serious adverse events

Adverse events will be recorded via Electronic CRDB (Clinical Records Database) using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of a fatal SAE/ or SUSAR and therefore requires immediate notification to the regulatory authority (FDA) and AstraZeneca/MedImmune Patient Safety in parallel within 5 calendar days; All other non-fatal or non-SUSAR SAE's can be sent to the regulatory agency and AstraZeneca within 10 days on a monthly basis.

The following variables will be collected for each AE:

- AE (verbatim)
- The date (and time when clinically relevant) when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not

- Investigator causality rating against durvalumab (yes or no)
- Investigator causality rating against TPIV200 + GM-CSF (yes or no)
- Action taken with regard to durvalumab
- Action taken with regard to TPIV200 + GM-CSF
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to TPIV200 + GM-CSF

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

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

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab or TPIV200, whichever is later).

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

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

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

17.2.1.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

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

17.2.1.3 Post study events

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

17.2.1.4 Reporting of serious adverse events

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

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

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox within 24 hours of notification:***
AEMailboxClinicalTrialTCS@astrazeneca.com and to the TapImmune Medical Director at pyeramian@tapimmune.com.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca, TapImmune, and the FDA.

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

17.2.1.5 Other events requiring reporting

Overdose

An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 11.4 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 11.4). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 11.4). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

Hepatic function abnormality

Hepatic function abnormality (as defined in Section 11.4) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 11.4 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

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

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

Pregnancy

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic

pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Pregnancy in a subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 17.2.1.4 for contact information) and to the TapImmune Medical Director.

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to AstraZeneca/MedImmune Patient Safety and to the TapImmune Medical Director or designee after outcome.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

- **Appendix A:** Durvalumab Dosing Modification and Toxicity Management Guidelines (Tables 1,2,3)
- **Appendix B:** Schedule of study procedures: follow-up for subjects who have completed durvalumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progression of disease
- **Appendix C:** Schedule of study procedures: follow-up for subjects who have discontinued durvalumab treatment due to confirmed progression of disease