PROTOCOL

TITLE:	Atezolizumab in Combination with Neoadjuvant Chemotherapy and Interval Cytoreductive Surgery for Patients with Newly-Diagnosed Advanced-Stage Epithelial Ovarian Cancer
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SUMMARY OF CHANGES

- **Protocol Version 3-9**
    - Changes to the protocol include addition of modifications for patients who cannot have surgery at the specified time point as required in the protocol, modification for bevacizumab timing based on ICS modifications, edits to the eligibility checklist, and addition of language for patients with a germline or somatic BRCA mutations in regards to participation and maintenance

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
anti-HBc	antibody to hepatitis B core antigen
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
BSA	body surface area
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRF	Case Report Form
CT	computed tomography
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	leucovorin, 5-fluorouracil, oxaliplatin
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	interval cytoreductive surgery
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
irAE	immune-related adverse event
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
irRC	immune-related response criteria

Abbreviation	Definition
IV	intravenous
LFT	liver function test
LPLV	last patient, last visit
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NACT	neoadjuvant chemotherapy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
pCR	pathologic complete response rate
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PES	polyethersulfone
PET	positron emission tomography
PFS	progression-free survival
PI	Package Insert
PK	pharmacokinetic
PR	partial response
PUVA	psoralen plus ultraviolet A radiation
PVC	polyvinylchloride
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UBC	urothelial bladder cancer
ULN	upper limit of normal
V_{ss}	volume at steady state

1. INTRODUCTION

1.1 Ovarian Cancer

Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States and Europe. The term “ovarian cancer” typically refers to a constellation of diseases including epithelial ovarian, fallopian, and peritoneal carcinomas. Within the US, approximately 24,000 women are diagnosed with ovarian cancer annually and 14,000 are expected to die each year of the disease [1]. While most women have an excellent response to first-line chemotherapy, the majority will experience disease recurrence and development of chemotherapy resistance, with increased susceptibility to disease-related complications, and death. Thus, there is a significant opportunity to improve long-term treatment outcomes through the safe integration of effective targeted interventions during primary therapy.

1.1.1 Current Management

Standard first-line therapy for the management of advanced-stage ovarian cancer is cytoreductive surgery followed by postoperative systemic chemotherapy consisting of a combination of a platinum and taxane agent, usually carboplatin and paclitaxel. Various Phase III studies have shown progression-free survival rates of 10 – 28 months using various routes of administration (i.e. intraperitoneal vs intravenous), sequence of chemotherapy and cytoreductive surgery (i.e. neoadjuvant vs postoperative), and the addition of other agents [2-10]. As of 2016, no universal strategy is preferred and the National Comprehensive Cancer Network endorses multiple options for front-line therapy [11].

Neoadjuvant Chemotherapy

Long-term clinical outcomes have been correlated with a number of prognostic factors, including stage, extent of residual disease following cytoreductive surgery, performance status, tumor grade, and presence of ascites. While the goal of primary cytoreductive surgery is resection of all macroscopic disease, not all patients are suitable candidates for aggressive primary surgery, based on distribution of disease, comorbidities, and other factors.

Over the last 10 years, there has been increased interest in a tailored approach involving neoadjuvant chemotherapy (NACT) with consideration of interval cytoreductive surgery (ICS) for individual patients who were not good candidates for primary cytoreductive surgery. Two phase III randomized trials have validated this approach for selected patients, based on minimization of perioperative complications with similar long-term clinical outcomes (PFS and OS) [9, 10]. By 2013, approximately 40% of patients at NCCN cancer centers received NACT-ICS [12]. It has also been recognized that NACT-ICS offers an important opportunity to evaluate new agents in combination with standard therapy, while

also providing access to pre- and post-treatment biospecimens to evaluate molecular targeting, immunoregulatory function, and tumor response.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor specific T cell responses, resulting in improved anti-tumor activity [13, 14]. Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and previously treated metastatic non-small cell lung cancer.

Refer to the atezolizumab Investigator's Brochure and the atezolizumab package insert for details on nonclinical and clinical studies, and safety data including immune-related adverse events.

1.2.1 Clinical Safety

Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness. Expected adverse drug reactions associated with atezolizumab include the following: hepatitis/transaminitis, hypothyroidism, infusion-related reactions (IRRs), pneumonitis, influenza-like illness, and dermatologic reactions. Potential adverse drug reactions include the following: anti-therapeutic antibodies (ATAs), colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion.

For further details, see the atezolizumab Investigator’s Brochure.

1.2.2 Drug Interactions

Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

1.3 Backbone Chemotherapy Regimen: Intravenous Carboplatin with Dose-dense Weekly Paclitaxel

1.3.1 Background

Relative efficacy and safety was considered in the determination of the backbone chemotherapy regimen for this trial. Intravenous carboplatin with dose-dense weekly paclitaxel was selected based on the outcomes of two recent phase III studies evaluating weekly dose-dense paclitaxel vs every 3 week paclitaxel scheduling on outcomes. JGOG 3016 showed an impressive improvement using the dose-dense versus every 3 week administration, respectively, in both PFS (28 vs 17 months, p=0.004) and OS (100.5 vs 62.2 months, p=0.04) [15]. GOG262 also compared weekly dose-dense paclitaxel to every 3 week paclitaxel administration specifically in a population of patients whose residual disease post-cytoreductive surgery was >1cm or who opted for NACT [3]. Overall, there was no difference between the two treatment arms, suggesting that the results may have been influenced by the use of bevacizumab in >80% of patients enrolled. Of note, among the 112 patients who elected not to receive bevacizumab, there was improved PFS in the subset assigned to weekly paclitaxel, compared to the subset assigned to every 3 week paclitaxel (14.2 vs 10.3 months, p=0.03).

Differences in patient selection, and baseline population characteristics, along with the large proportion of patients who received primary bevacizumab in GOG 262 may account for the differences between the two studies. In addition, within Japan, bevacizumab was not generally available for management of disease post-progression, while patients within the US would generally have access to commercial bevacizumab.

There are additional details that further influenced the choice of chemotherapy for this trial. First, in GOG 262, 13% of patients elected to receive NACT followed by ICS and there were no safety issues identified. In addition, there was no apparent impact of the paclitaxel schedule on PFS in patients opting for NACT-ICS versus primary cytoreduction. Second, maximal benefit of the weekly dose-dense paclitaxel regimen in JGOG3016 was seen in patients with more advanced suboptimal disease, a population that would be anticipated to be similar to the planned population for this study.

From the perspective of feasibility, the dose-dense weekly regimen has been widely adopted at our centers following publication in 2013. Finally, this regimen offers two specific design advantages for the current trial: 1) more frequent opportunities for patient safety assessment during combination therapy, and 2) decreased prophylactic steroid requirement for weekly paclitaxel dosing. In view of the limited number of patients, as well as the potential influence of a specific chemotherapy regimen on efficacy and toxicity, the chemotherapy regimen will be held consistent across the entire study population.

1.3.2 **Safety Profile**

The most common dose-limiting adverse events associated with carboplatin and weekly dose-dense paclitaxel are hematologic. Frequency of grade 3 or greater adverse events by treatment group are listed in the tables below for GOG262 (Table 1.3.2a) and JGOG3016 (Table 1.3.1b). In both studies, anemia was the only grade 3 or greater hematologic toxicity significantly worse in the dose-dense paclitaxel group. The risk of febrile neutropenia was not increased in either study. Overall, the dose-dense weekly paclitaxel regimen is well tolerated and its toxicity profile does not significantly overlap with the potential toxicities of atezolizumab.

Table 1.3.2a Selected Grade 3 or Greater Toxicities Reported in GOG262

	Number (Percentage) of Grade 3-4 Adverse Events		
Adverse Event	Weekly Paclitaxel N=340	Q3Week Paclitaxel N=343	p-value
Anemia	124 (37)	54 (16)	<0.001
Diarrhea	23 (7)	11 (3)	0.03
Fatigue	NR	NR	
Febrile Neutropenia	13 (4)	16 (5)	0.58
Nausea	20 (6)	11 (3)	0.10
Neuropathy (Motor)	3 (1)	3 (1)	0.99
Neuropathy (Sensory)	9 (3)	7 (2)	0.61
Neutropenia	246 (72)	286 (83)	<0.001
Thrombocytopenia	67 (20)	54 (16)	0.18
Vomiting	19 (6)	15 (4)	0.47

Table 1.3.1b Grade 3 or Greater Toxicities Reported in JGOG 3016

	Number (Percentage) of Grade 3-4 Adverse Events		
Adverse Event	Weekly Paclitaxel N=312	Q3Week Paclitaxel N=314	p-value
Anemia	214 (69)	137 (44)	<0.0001
Diarrhea	10 (3)	8 (3)	0.64
Fatigue	15 (5)	8 (3)	0.14
Febrile Neutropenia	29 (9)	29 (9)	1.00
Nausea	32 (10)	36 (11)	0.70
Neuropathy (Motor)	15 (5)	20 (6)	0.56
Neuropathy (Sensory)	21 (7)	20 (6)	0.87
Neutropenia	286 (92)	276 (88)	0.15
Thrombocytopenia	136 (44)	120 (38)	0.19
Vomiting	9 (3)	11 (4)	0.82

1.4 STUDY RATIONALE

A combination of carboplatin and paclitaxel remains the most widely used first-line treatment option for patients with advanced-stage ovarian cancer. While optimized chemotherapy, cytoreductive surgery, high-resolution imaging, and better supportive care have contributed to improved clinical outcomes, this appears to have reached a plateau, without a change in disease-related mortality. This provides an important opportunity to integrate novel treatment interventions, such as immunotherapy, with primary treatment.

Tumor cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared to standard chemotherapy alone. Furthermore, PD-L1 expression is frequently increased on the surface of ovarian cancer cells and is thought to contribute to immune evasion.

Limited data are available regarding the clinical activity of PD-1 and PD-L1 inhibitors in ovarian cancer. Among patients with platinum-resistant recurrent disease and multiple prior therapies, response rates from small phase I-II studies have been reported between 10-15% [16-18]. However, due to extensive prior treatment, and limited immunologic capacity, these studies may underestimate the true proportion of patients that might benefit from these interventions.

Evaluation of these agents in patients without prior therapy should maximize the opportunity to achieve clinical benefit while minimizing the risk of treatment-related complications. We proposed to conduct a non-randomized trial of atezolizumab in combination with primary NACT-ICS followed by maintenance

atezolizumab for patients with untreated advanced-stage high-grade epithelial ovarian cancer (EOC) to validate a safe dose of the combination over multiple cycles of chemotherapy and cytoreductive surgery in women with advanced ovarian cancer.

In December 21, 2018 the interim analysis of the Phase III JAVELIN Ovarian 100 study comparing to incorporation of avelumab, a PD-L1 inhibitor, with paclitaxel and carboplatin in women with newly diagnosed ovarian cancer would did not be superior compared to platinum-based therapy alone [23]. Given these findings we propose to allow the option of bevacizumab after debulking surgery.

On June 13, 2018, the Food and Drug Administration approved bevacizumab (Avastin, Genentech, Inc.), a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, for stage III or IV disease after initial surgical resection [24].There is data to support the combination of anti-VEGF therapy and immunotherapy. VEGF may decrease T cell infiltration [25] and thus VEGF inhibition may enhance intratumoral T-cell recruitment. This hypothesis has been tested in renal cell carcinoma (RCC). The combination of bevacizumab and atezolizumab in RCC led to increased CD8+ tumor-infiltrating lymphocytes and enhanced tumor reduction [26]. Bevacizumab may also promote T cell infiltration and immune-mediated tumor cell kill by normalizing tumor-associated vasculature [27].

Patients will be treated with paclitaxel, carboplatin, and atezolizumab for cycles 1-3. Interval surgery will occur after Cycle 3. Within 6 weeks after interval surgery or when clinically appropriate patients will resume concurrent chemotherapy and atezolizumab. For cycle 5, patients have the option to include bevacizumab into their treatment regimen as per FDA approval. Those who opt for bevacizumab will receive chemotherapy, atezolizumab, and bevacizumab (15 mg/kg IV every 3 weeks). Selection of patients for bevacizumab and treatment with this therapy will be performed as per institutional guidelines. Atezolizumab is being evaluated with chemotherapy and bevacizumab in the randomized phase III GOG3015 trial. GOG3015 includes an independent data monitoring committee and no significant safety concerns have been reported.

Upon completion of concurrent therapy, patients will commence maintenance treatment with either atezolizumab alone or with bevacizumab and atezolizumab based on investigator and patient preference.

2. OBJECTIVES

2.1 PRIMARY

To validate a safe dose of the combination of atezolizumab with weekly dose-dense paclitaxel and carboplatin when delivered over multiple cycles of NACT

with planned ICS (henceforth referred to as NACT-ICS), followed by concurrent paclitaxel, carboplatin, and atezolizumab +/- bevacizumab, followed by maintenance atezolizumab +/- bevacizumab in women with advanced ovarian cancer, as measured by frequency and severity of adverse events by Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

2.2 SECONDARY

To estimate objective response rate (ORR), pathologic complete response rate (pCR) at interval cytoreduction, PFS, and OS in the study population.

2.3 TRANSLATIONAL

Primary Translational: To correlate clinical outcomes (in particular median PFS) with PD-L1 expression.

Secondary Translational: To correlate clinical outcomes (in particular median PFS) with tumor-infiltrating lymphocyte subpopulations, immune checkpoint receptor profiles, gene expression profiles associated with immunoactivation, cytokine expression profiles, *BRCA* mutation status, and tumor mutation profile.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase IB non-randomized, single-arm, open-label study of atezolizumab in combination with primary NACT-ICS in patients with advanced-stage epithelial ovarian cancer. The target population is women with previously untreated epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) with advanced stage (FIGO III-IV) disease suitable for NACT and ICS. The following regimen will be administered every 3 weeks for 3 cycles prior to ICS, then for 3 cycles following ICS:

- Carboplatin AUC = 5 or 6 IV, D1 of each cycle
- Paclitaxel 70 to 80 mg/m2 IV, over one hour, on D1, 8, 15 of each cycle
- Atezolizumab 1200 mg IV D1 of each cycle of chemotherapy and will be continued as maintenance therapy every 3 weeks until there is a lack of clinical benefit, unacceptable toxicity, or a total duration of 22 cycles (6 concurrent with chemotherapy and 16 maintenance cycles).
- Bevacizumab (15 mg/kg IV every 3 weeks) may be added at cycle 5 of chemotherapy as per FDA approval. Those who opt for bevacizumab will receive chemotherapy, atezolizumab, and bevacizumab for cycles 5 and 6 followed by atezolizumab and bevacizumab maintenance. Maintenance bevacizumab will be given for a total duration of 16 cycles. Patients who have completed chemotherapy may opt for bevacizumab in the

maintenance setting only if the amendment to add bevacizumab was not approved before after they started maintenance therapy.
- Upon completion of concurrent chemotherapy and atezolizumab therapy, patients will commence maintenance treatment with atezolizumab + bevacizumab for a total of up 16 cycles of maintenance therapy (22 total cycles of atezolizumab, and 18 total cycles of bevacizumab).

Each cycle is 21 days in duration and will be administered in the outpatient setting. Limited individualized flexibility in dose assignment (as noted) is permitted per physician discretion in regards to advanced-stage disease, nutritional status, ascites, non-physiologic creatinine measurements, and other comorbidities.

Three cycles of NACT with atezolizumab will be administered every 3 weeks prior to ICS (occurring between cycles 3 and 4) followed by 3 additional cycles (cycles 4-6) of chemotherapy with atezolizumab. The addition of bevacizumab at cycle 5 is optional. Surgery must be performed after the third course of chemotherapy as soon as nadir counts permit, but preferably within six weeks after the completion of the third chemotherapy cycle. Fourth cycle of chemotherapy is to be administered as soon as possible, but preferably no more than six weeks after ICS.

Safety monitoring, including assessment for irAEs, will occur at each cycle and for 90 days after the last administration of atezolizumab or until start of next anti-cancer regimen, whichever occurs first. Image assessment by CT scan or MRI will be performed at baseline, prior to ICS to assess response, after completion of 6 cycles of chemotherapy with atezolizumab to assess response at end of treatment, and as clinically indicated during the maintenance phase and after completion of study treatment to assess PFS. Disease progression/recurrence will be defined per RECIST criteria and will not include isolated asymptomatic progression on the basis of CA125 levels. Immune function analysis will be performed on blood and tumor samples obtained at two time points: 1. confirmatory biopsy prior to start of therapy and 2. ICS.

It is estimated that 40 patients will be enrolled at an accrual rate of 3-5 patients/month and followed for a median of 3 years.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or safety follow-up is received from the last patient, whichever

occurs later. Safety follow-up is expected to occur 27.5 months after enrollment opens. LPLV is dependent on time to progression. Median time to progression after completion of chemotherapy is estimated to be ~12 months.

3.3 RATIONALE FOR STUDY DESIGN

NACT-ICS offers an opportunity to evaluate new agents in combination with standard therapy, while also providing access to pre- and post-treatment biospecimens to evaluate molecular targeting, immunoregulatory function, and tumor response. The study is designed to obtain safety data for atezolizumab when combined with carboplatin and weekly dose-dense paclitaxel NACT-ICS. Evaluating the safety of the combination in this setting will enable future tests of the hypothesis that the combination will result in more profound and durable responses, in larger randomized trials. The addition of bevacizumab in select patients will expand information on the safety, and anti-tumor activity of combination chemotherapy, atezolizumab, and bevacizumab.

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measure

Safety/tolerability of the combination of atezolizumab + NACT-ICS, followed by atezolizumab + chemotherapy +/- bevacizumab, followed by maintenance atezolizumab +/- bevacizumab will be assessed using the following primary safety outcome measures:

- Ability to undergo planned ICS (when clinically indicated) within 6 weeks of last dose of NACT,
- Incidence, nature, and severity of adverse events and laboratory abnormalities as measured by frequency and severity of adverse events by NCI CTCAE v5.0,
- Additional safety outcome measures will include the number of cycles and the dose intensity including starting dose and dose modifications of each component of the treatment regimen during and following the period of protocol-directed therapy.

3.4.2 Secondary Activity Outcome Measures

The following activity outcome measures will be assessed:

- Response rate
- Pathologic complete remission rate (at ICS)
- PFS
- OS

Response/progression will be determined using RECIST v1.1 (see Appendix 4) and irRC (see Appendix 5).

3.4.3 Pharmacodynamic/Translational Outcome Measures

1. Quantitation of pre- and post-treatment changes in:
   - PD-L1 expression
2. Correlation of above markers, *BRCA* mutation status, and tumor mutation profile with clinical outcomes
   - tumor-infiltrating lymphocyte subpopulations
   - immune checkpoint receptor profiles
   - gene expression profiles associated with immunoactivation
   - cytokine expression profiles
   - angiogenic markers

4. MATERIALS AND METHODS

4.1 STUDY POPULATION

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability and willingness to comply with the requirements of the study protocol
- Age ≥ 18 years
- No prior treatment for primary advanced (stage III or IV) epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
- Confirmation of diagnosis and patients for whom the plan of management will include NACT followed by ICS. The decision to proceed with NACT will be at the treating physician's discretion and include patients with advanced stage disease considered at low likelihood for optimal cytoreduction with primary debulking surgery.
- All patients must have measurable disease per RECIST v1.1 (see Appendix 4). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ⩾ 10mm when measured by CT, MRI or caliper measurement by clinical exam; or ⩾ 20mm when measured by chest x-ray. Lymph nodes must be ⩾ 15mm in short axis when measured by CT or MRI.

Patients must meet the following criteria prior to initiation of study treatment:

- Histology consistent with high-grade epithelial ovarian cancer (excluding mucinous carcinoma and clear cell carcinoma)
- An adequate pre-treatment tumor biopsy is required for the translational research component. Acceptable options include laparoscopic biopsy or image-guided core needle biopsy (minimum of two cores). Fine needle aspiration (FNA) biopsy or cytology from ascites may be adequate at the discretion of the sponsor.
    - *Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen of the types listed above only upon agreement of the sponsor.*
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):
    - ANC $\geq$ 1500 cells/μL
    - Lymphocyte count $\geq$ 300/μL
    - Platelet count $\geq$ 100,000/μL
    - Hemoglobin $\geq$ 9.0 g/dL
    - Total bilirubin $\leq$ 1.5 $\times$ upper limit of normal (ULN) with the following exception:

      Patients with known Gilbert disease who have serum bilirubin level $\leq$ 3 $\times$ ULN may be enrolled.
    - AST and ALT $\leq$ 3.0 $\times$ ULN with the following exception:

      Patients with liver involvement: AST and/or ALT $\leq$ 5 $\times$ ULN
    - Alkaline phosphatase $\leq$ 2.5 $\times$ ULN with the following exceptions:

      Patients with documented liver involvement or bone metastases: alkaline phosphatase $\leq$ 5 $\times$ ULN or

      Patients with isolated $\leq$ 5 $\times$ ULN with elevation AST, ALT, or bilirubin
    - Creatinine clearance $\geq$ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

      $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$
    - INR and aPTT $\leq$ 1.5 $\times$ ULN

      This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low-molecular-weight heparin or warfarin) should be on a stable dose.

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 (see Appendix 6)
- Peripheral neuropathy less than or equal to CTCAE Grade 1
- For female patients of childbearing potential, agreement (by patient) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly) and to continue its use at least until ICS or if ICS is not performed then 90 days post last dose of atezolizumab
- Patients who opt to receive bevacizumab must meet standard institutional treatment guidelines

4.1.2 **Exclusion Criteria**

Patients who meet any of the following criteria will be excluded from study entry.

General Exclusion Criteria:

- Prior systemic chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.
    - Exceptions include basal cell or squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- AEs from prior anticancer therapy that have not resolved to Grade ≤ 1 except for alopecia
- Bisphosphonate therapy for symptomatic hypercalcemia
    - Use of bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) is allowed.
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease
- Known primary central nervous system (CNS) malignancy or symptomatic CNS metastases
- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies
- Inability to comply with study and follow-up procedures
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy,

Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis

  - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
  - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
  - Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

    Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations

    Rash must cover less than 10% of body surface area (BSA)

    Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

    No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection
  - Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
  - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
  - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

Medication-Related Exclusion Criteria:

- Prior history of treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA4 or any other antibodies targeting co-stimulation or checkpoint pathways
- Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN]-α or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1
  - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation

4.2 STUDY TREATMENT

4.2.1 Study Drug: Atezolizumab

Once marketing authorization is received commercial atezolizumab will be used and will not be provided by Genentech for “on-label” studies. For studies done before marketing authorization and/or "out of label", atezolizumab will be provided free of charge by Genentech but switched to commercial drug once marketing authorization is received. Genentech will replace any atezolizumab drug that is not reimbursed. For studies done “out of label,” atezolizumab will be provided free of charge by Genentech. The Sponsor-investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Genentech requirements.

4.2.1.1 Formulation and Storage

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C – 8°C (36°F – 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the atezolizumab Investigator’s Brochure.

4.2.2 Protocol-Specified Chemotherapy

Carboplatin, paclitaxel, with or without bevacizumab will be administered according to the dose and schedule listed in Section 4.2.3.

4.2.2.1 **Formulation and Storage**

Sites will obtain carboplatin, paclitaxel, with or without bevacizumab through commercial supply and must refer to the package insert for detailed pharmacologic, storage, and safety information.

4.2.3 **Dosage, Schedule, Administration, and Premedications**

On days of scheduled atezolizumab, carboplatin, paclitaxel, with or without bevacizumab chemotherapy is to be administered, in the following manner:

1. Paclitaxel 70-80 mg/m2 IV administered over approximately one hour followed by

2. Carboplatin IV administered over 15-30 minutes to achieve an initial target AUC of 5-6 mg/mL/Min (Calvert formula dosing) followed by

3. For patients who elect to receive bevacizumab, bevacizumab will be given 15 mg/kg IV administered over 90 (± 15) minutes for the first infusion. If previous infusion is well tolerated by patient, then infusion period may be reduced to 60 (± 10) minutes. The infusion period time can be reduced to 30 (± 10) minutes for subsequent infusions dependent on patient tolerability.

4. Atezolizumab 1200 mg administered over 60 (± 15) minutes for the first infusion. If previous infusion is well tolerated by patient, then infusion period may be reduced to 30 (± 15) minutes for subsequent infusions

Sites should follow their institutional standard of care for determining chemotherapy dose for obese patients and for dose adjustments in the event of patient weight changes.

Carboplatin, paclitaxel, with or without bevacizumab will be administered per local institution standards with the following pre-medications administered prior to paclitaxel infusion:

- an H1 blocker (such as diphenhydramine, loratadine, or fexofenadine) and

- an H2 blocker (such as ranitidine or cimetidine).

- Because steroids may attenuate the beneficial effect of atezolizumab, corticosteroid pre-medication will be minimized when possible (refer to Section 4.3.1 Concomitant Therapy). It is recommended that dexamethasone 10mg IV be administered prior to paclitaxel during cycle 1D1. If there is no evidence of hypersensitivity reaction, dexamethasone should be reduced to 5 mg on C1D8 and omitted beginning with C1D15, unless hypersensitivity develops. Hypersensitivity reactions and

subsequent chemotherapy treatments should be managed according to institutional standards. In cases of atezolizumab related toxicity, steroids may be administered at the discretion of the treating investigator.

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [± 2] days). Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [Kehoe, #8]). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion associated AEs, subsequent infusions can be delivered over 30 (± 10) minutes. Vital signs should be collected according to institutional standards during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix 7.

Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided in Section 4.6 and Section 4.4.2, respectively.

4.3 CONCOMITANT AND EXCLUDED THERAPIES

4.3.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms related to atezolizumab may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 7).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$ 2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.1.2) should continue their use. Females of reproductive potential should use highly effective means of contraception.

4.3.2 Excluded Therapy

Any concomitant therapy, other than outlined within the protocol, intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use

may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity.

- The use of a RANKL inhibitor (denosumab) must be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab.

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

4.4 GENERAL PLAN TO MANAGE SAFETY CONCERNS

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2) and close monitoring (as indicated below and in Section 4.8.2). See Section 6.3.2 for complete details regarding safety reporting for this study.

Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account (see Section 4.1.2).

Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Patients will be followed for safety for 90 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 for the list and timing of study assessments). All serious adverse events (SAEs) and protocol-defined events of special interest (see Section 6.2.2) will be reported in an expedited fashion (see Section 6.3). In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

4.4.1 Dose Modification of Chemotherapy

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events will be graded according to the NCI CTCAE v5.0 grading system.

Dose modifications and interruptions should proceed in accordance with good clinical practice and institutional applicable guidelines (See Appendix 13 for Dose Modifications and Day 1 Dosing Criteria for hematologic dosing modifications). Patients enrolled may use colony stimulating factors, such as granulocyte colony-stimulating factor (G-CSF) and erythropoietin, per guidelines of the American Society of Clinical Oncology (ASCO) and ASCO/American Society of Hematology (ASH) guidelines, respectively [19, 20]. Evidence supporting the use of long-acting (pegylated) forms of G-CSF in patients receiving weekly chemotherapy is limited, thus preference should be given to conventional formulations of G-CSF. Use of G-CSF is at the discretion of the treating physician.

When treatment is temporarily interrupted because of toxicity caused by chemotherapy, treatment cycles will be restarted such that the atezolizumab infusions remain synchronized and aligned with the chemotherapy schedule.

If chemotherapy is discontinued secondary to toxicity, the patient may continue to receive atezolizumab as long as she is experiencing clinical benefit in the opinion of the investigator.

Dosing for bevacizumab will be based on institutional standards.

4.4.2 Management of Specific Safety Concerns with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as

autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNFα inhibitors.

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening irAEs.

4.4.3 Guidelines for Atezolizumab Dosage Modification, Treatment Interruption, or Discontinuation

Atezolizumab treatment will be given until there is unacceptable toxicity, lack of clinical benefit, or a total duration of 22 cycles.

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for $>$ 84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 6.3.1.

If a patient must be tapered off steroids used to treat AEs, atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of $\leq$ 10 mg/day. Post treatment steroids to reduce atezolizumab related adverse events are acceptable based on investigator discretion. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Sponsor.

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNFα inhibitors.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

The atezolizumab Investigator's Brochure and the National Comprehensive Cancer Network (NCCN) guidelines provide guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-related pulmonary, hepatitic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, neurologic, and meningoencephalitis events. The decision to withthold or discontinue atezolizumab may be made at the discretion of the investigator per the guidelines in the atezolizumab Investigator's Brochure, NCCN Guidelines, or Institutional guidelines. Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented in this section as they have been observed in prior studies and are potentially immune related. See Section 4.4.3 for guidelines for the management of IRRs (see Appendix 7 for precautions for anaphylaxis).

Further information regarding adverse event management is provided. Management can be based on atezolizumab Investigator’s Brochure, NCCN guidelines, and institutional guidelines at the discretion of the investigator. Data regarding immune related adverse events are increasing and management options are evolving. The incorporation of all these resources allow the investigator to use the most current management guidelines.

4.4.3.1 **Gastrointestinal Toxicity**

Immune-mediated colitis has been associated with the administration of atezolizumab.

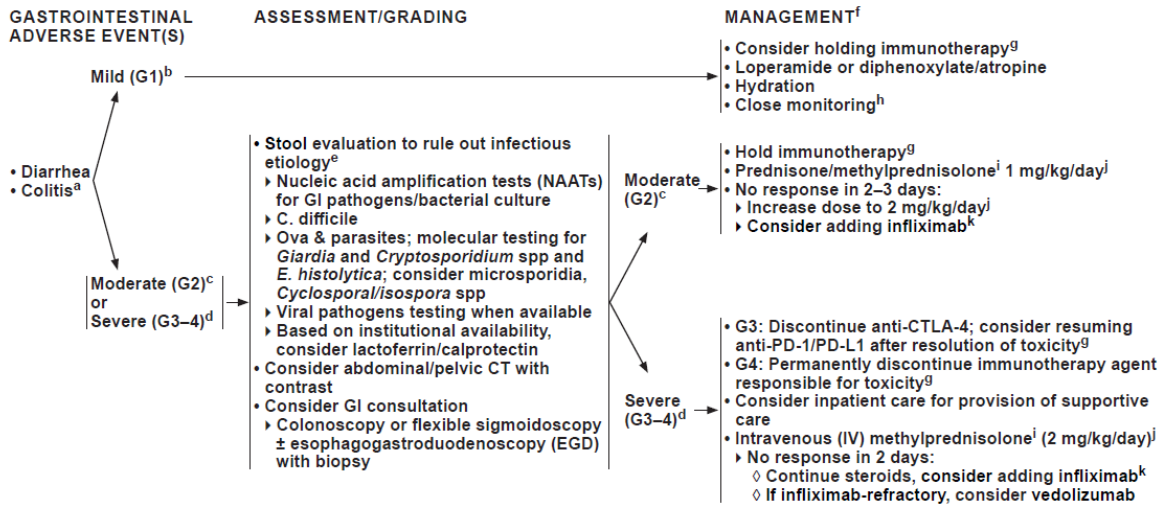
Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy is recommended. Ideally three to five specimens for standard paraffin block should be performed with one or two biopsy specimens snap frozen and stored if possible.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose ≤ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea. Table 4.4.3.1 provides a summary of dose modification guidelines for gastrointestinal toxicities that may be used at investigator discretion.

Table 4.4.3.1 Dose Interruption Guidelines for Gastrointestinal Toxicity

*Immunotherapy is atezolizumab



[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever. Blood in the stools and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including peptic ulcer disease (PUD) and malignant bleeding.
[b] Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[c] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[d] More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
[e] It is not necessary to wait for test results before providing therapy to manage immune-related adverse events (irAEs).
[f] See Principles of Immunosuppression (IMMUNO-A).
[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] If progressive, consider stool evaluation to rule out infectious etiology.
[i] Convert to prednisone when appropriate.
[j] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[k] Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment. (See Principles of Immunosuppression [IMMUNO-A] regarding TB testing.)

4.4.3.2 **Hepatotoxicity**

Immune-mediated hepatitis has been associated with the administration of atezolizumab.

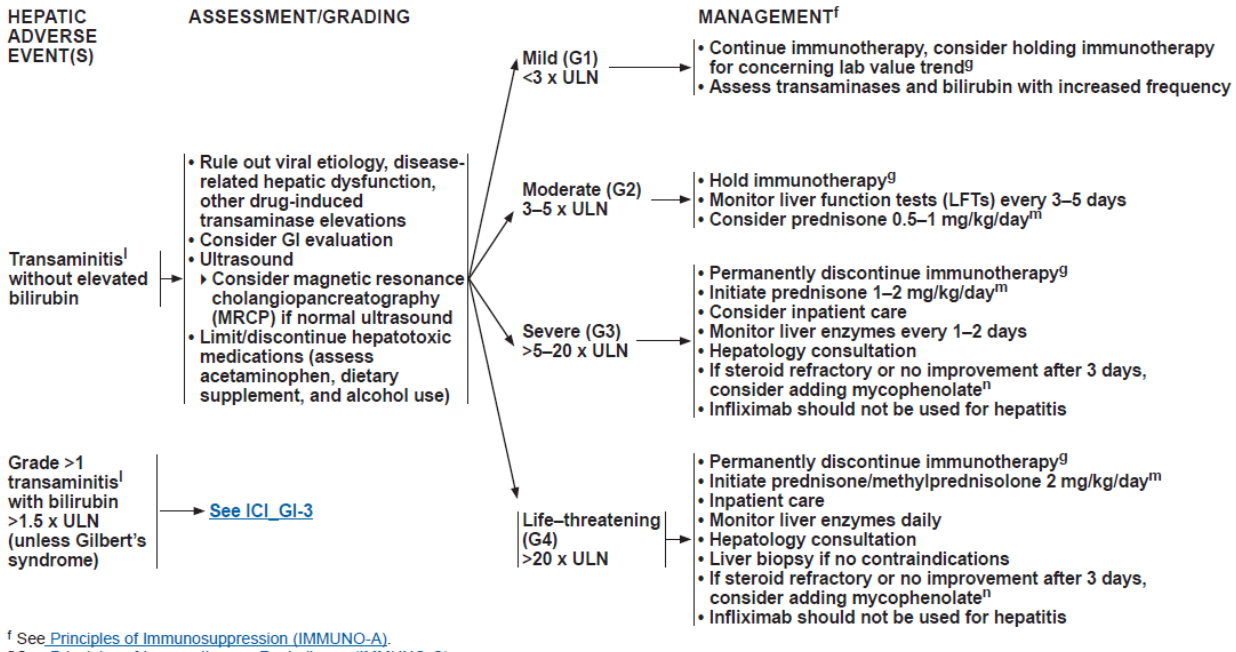
While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes of increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Patients with LFT abnormalities may be managed according to the guidelines in Table 4.4.3.2. at the discretion of the investigator.

Table 4.4.3.2 Dose Interruption Guidelines for Hepatotoxicity

*Immunotherapy is atezolizumab



[f] See Principles of Immunosuppression (IMMUNO-A).
[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] Elevated alanine transaminase (ALT) and aspartate transaminase (AST).
[m] When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.
[n] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

Table 4.4.3.2Dose Interruption Guidelines for Hepatotoxicity (cont.)

HEPATIC ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[f]
Grade >1 transaminitis[l] with bilirubin >1.5 x ULN (unless Gilbert's syndrome)	• Rule out viral etiology, disease-related hepatic dysfunction, other drug-induced transaminase elevations • Consider GI evaluation • Limit/discontinue hepatotoxic medications (assess acetaminophen, dietary supplements, and alcohol use)	• Permanently discontinue immunotherapy[g] • Initiate prednisone/methylprednisolone 2 mg/kg/day[m] • Inpatient care • Monitor liver enzymes daily • Hepatology consultation • If steroid refractory or no improvement after 3 days, consider adding mycophenolate[n] • Infliximab should not be used for hepatitis

[f] See Principles of Immunosuppression (IMMUNO-A).
[g] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[l] Elevated ALT and AST.
[m] When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month. Re-escalate as needed.
[n] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

4.4.3.3 **Dermatologic Toxicity**

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

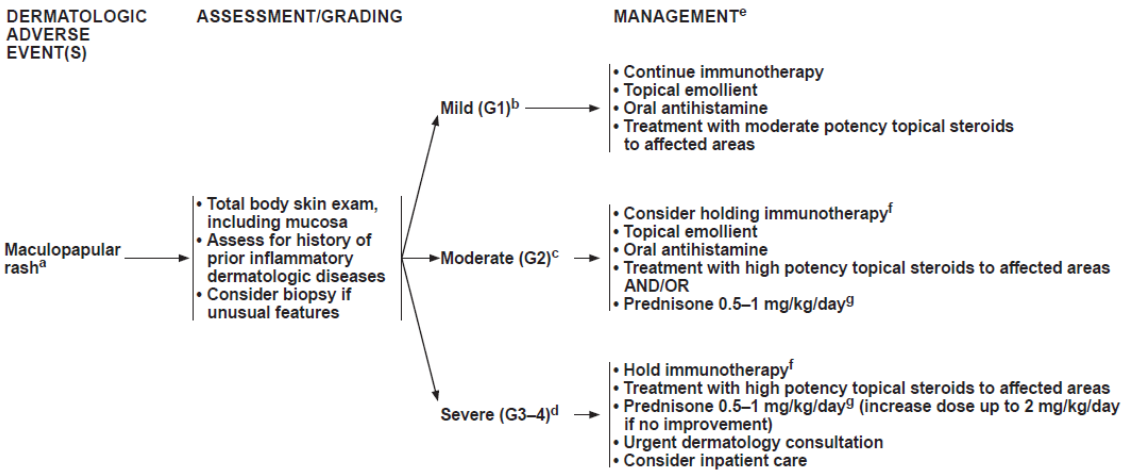
Management of the skin rash may be performed based on guidelines and in Table 4.4.3.3 as well as per institutional standards. Consider alerting a dermatologist at your center so that patients can be seen quickly in the event of development of the rash which may occur suddenly. A skin biopsy may be helpful to further evaluate the etiology of the rash. For maculopapular rash on face, consider alclometasone 0.05% cream BID. For maculopapular rash on body, consider clobetasol 0.05% cream BID.

For body fold rash, consider triamcinolone 0.1% cream plus Silvadene 1% mixed 1:1 and applied BID.

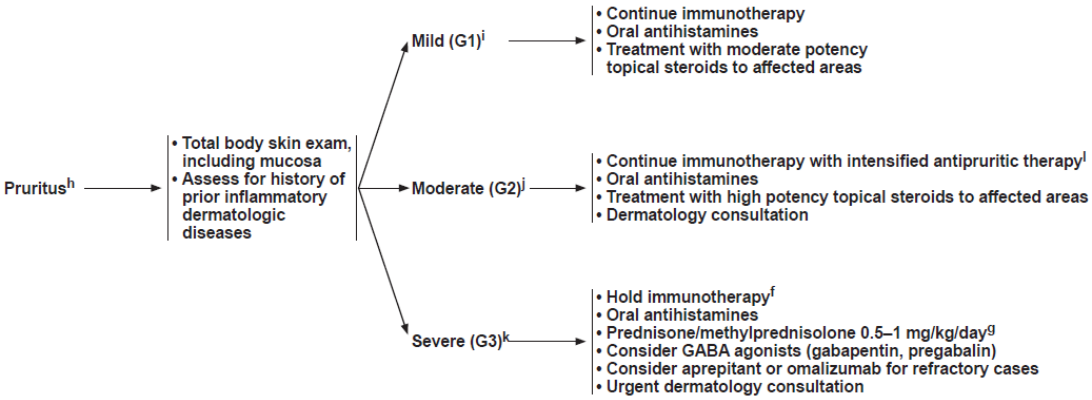
For pruritis grade 1, consider antipruritics such as hydroxyzine, cetirizine, diphenhydramine, loratadine, etc. For pruritis grade 2 or 3, antipruritics and consider Lyrica 25-50 mg BID, can increase as needed/tolerated up to 450 mg a day.

Table 4.4.3.3 Dose Interruption Guidelines for Dermatologic Toxicity

*Immunotherapy is atezolizumab

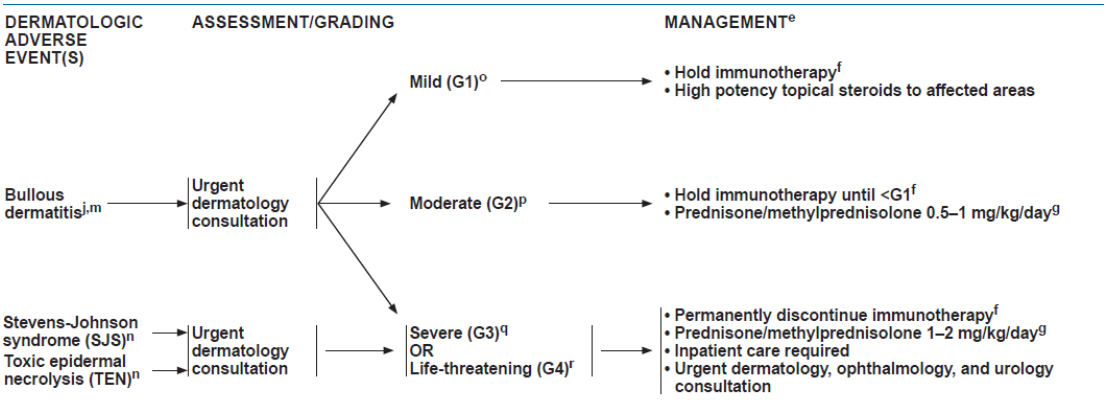


[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events (AEs), frequently affecting the upper trunk, spreading centripetally and may be associated with pruritus.
[b] Macules/papules covering <10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness).
[c] Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (iADLs).
[d] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care activities of daily living (ADLs).
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.



[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] Characterized by an intense itching sensation.
[i] Mild or localized.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[k] Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.
[l] Consider holding in select cases.

Table 4.4.4 Dose Interruption Guidelines for Dermatologic Toxicity (cont.)



[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[m] Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.
[n] Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) should be treated as grade 3–4 bullous dermatitis. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
[o] Asymptomatic; blisters covering <10% BSA.
[p] Blisters covering 10%–30% BSA; painful blisters; limiting iADLs.
[q] Blisters covering >30% BSA; limiting self-care ADLs.
[r] Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; intensive care unit (ICU) care or burn unit indicated.

4.4.3.4 Endocrine Toxicity

Hypothyroidism and hyperthyroidism has been associated with the administration of atezolizumab.

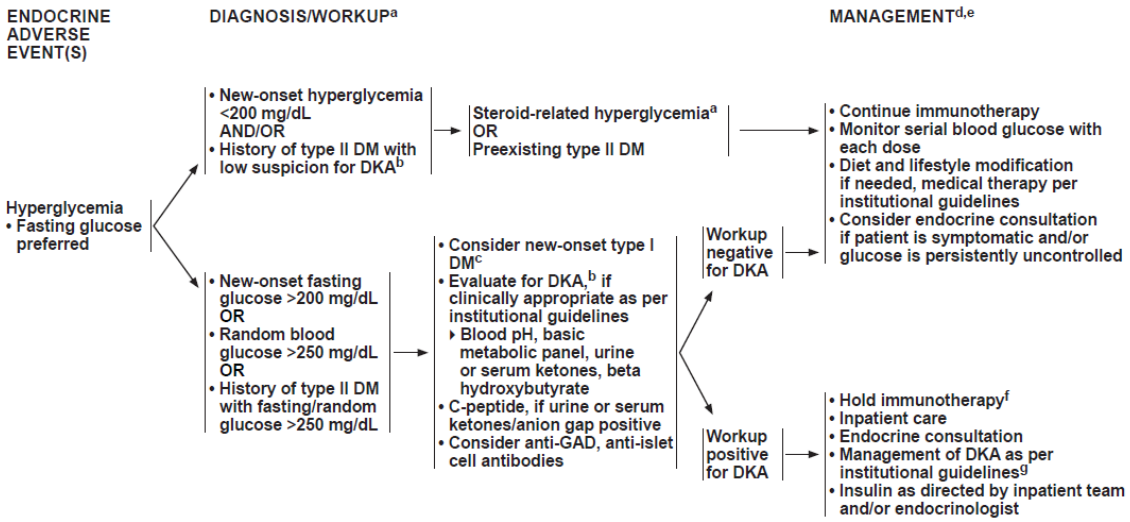
Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy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

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

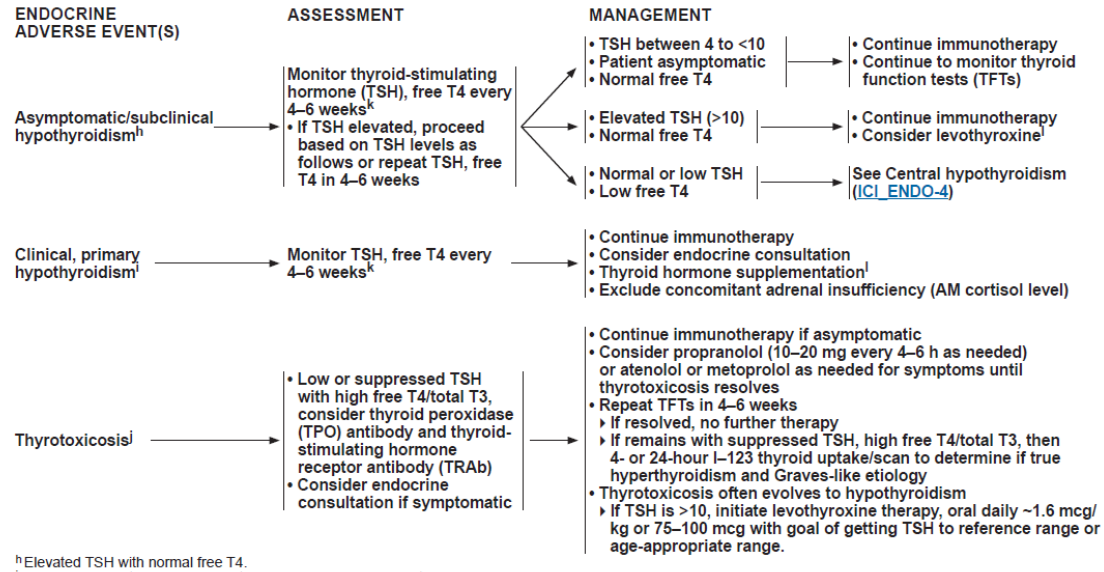
Hypothyroidism may be managed according to guidelines and in Table 4.4.3.4.as well as per institutional standards.

Table 4.4.3.5 Dose Interruption Guidelines for Endocrine Toxicity

*Immunotherapy is atezolizumab



[a] High-dose corticosteroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.
[b] Symptoms of diabetic ketoacidosis (DKA) may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.
[c] The development of type I DM is rare (1%–2%) but can be life-threatening if insulin therapy is not provided. Once new type I DM is diagnosed, management and monitoring should be directed by endocrinology team.
[d] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed.
[e] Insufficient evidence to suggest corticosteroids may reverse type I DM induced by immunotherapy, and may complicate glycemic control.
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Institutional guidelines may include but are not limited to: IV fluids +/– potassium supplementation, IV insulin, hourly glucose, serum ketones, blood pH, and anion gap.



[h] Elevated TSH with normal free T4.
[i] Generally, elevated TSH (>10) with low free T4, clinical symptoms.
[j] Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis.
[k] For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12–18 weeks as indicated.
[l] Levothyroxine oral daily ~1.6 mcg/kg with goal of getting TSH to reference range or age-appropriate range; reduce dose by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (eg, elderly populations or patients with comorbidities).

Table 4.4.3.6 Dose Interruption Guidelines for Endocrine Toxicity (cont.)

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[n,o]

Primary adrenal insufficiency[m]	• Evaluate cortisol level (AM)
	• Comprehensive metabolic panel (Na, K, CO_2, glucose), renin level
		• Endocrine consultation
		  ▸ Endocrine evaluation prior to surgery or any procedure
		• Hold immunotherapy[f]
		• Start corticosteroid first before other hormone replacement to avoid adrenal crisis
		• Steroid replacement[p,q]
		  ▸ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms[r]
		  OR
		  ▸ Prednisone 7.5 mg or 10 mg starting dose, then reduce to 5 mg daily as appropriate
		  AND
		  ▸ Fludrocortisone can be started 0.1 mg every other day; then titrated up or down based on blood pressure, symptoms, lower-extremity edema, and labs
		• If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids
		• Patients with severe symptoms (hypotension) may require additional fluids (eg, normal saline often >2 L required)
		• Patient education regarding stress doses of hydrocortisone for infection, trauma, etc.
		  ▸ Alert bracelet is recommended

[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[m] Low morning cortisol (<5) with high ACTH (> reference range) with or without abnormal electrolytes and symptoms. Other criteria: 30- or 60-minute cortisol <18 after ACTH stimulation in the setting of low morning cortisol and high ACTH. Other abnormalities: hypotension, orthostatic hypotension, low Na, and high K.
[n] See Principles of Immunosuppression (IMMUNO-A).
[o] If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[p] If acutely ill, double or triple these doses for 24–48 hours (ie, sick day rules for fever >101, nausea/emesis, surgeries).
[q] Will require physiologic replacement steroids indefinitely.
[r] The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. For many patients, this may be, for example, 10 mg in AM and 5 mg in PM, if tolerated.

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[n]
Central hypothyroidism[s]	• Evaluate cortisol (AM), FSH, LH, TSH, free T4, DHEA-S • Estradiol testing in women • Testosterone testing in men • Consider MRI of pituitary if confirmed central thyroid/ adrenal insufficiency	• Consider holding immunotherapy until no longer symptomatic[f] • Treat as hypophysitis (below)
Hypophysitis[t]	• Evaluate cortisol (AM), FSH, LH, TSH, free T4, testosterone in men, estrogen in premenopausal women • MRI brain ± contrast with pituitary/sellar cuts, if symptomatic	• Consider endocrine consultation • Hold immunotherapy until acute symptoms resolve[f,t] • If symptomatic, prednisone/methylprednisolone 1–2 mg/kg/day[o] • Hormone replacement as indicated[u] • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ▸ Alert bracelet is recommended

[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[n] See Principles of Immunosuppression (IMMUNO-A).
[o] If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[s] Low or suppressed TSH with inappropriately low free T4 may represent sequela of hypophysitis; for which other pituitary axes may be affected. Follow free T4 for thyroid replacement in the setting of hypophysitis–induced loss of TSH production.
[t] Hypophysitis may present with acute symptoms such as headache, photophobia, dizziness, nausea/emesis, fevers, anorexia, visual field cuts, or severe fatigue. Tests may show low ACTH, low AM cortisol, low Na, low K, low testosterone, and DHEA-S. Non-acute symptoms may include fatigue and possible weight loss.
[u] Hormone replacement for pituitary damage should include steroid replacement (hydrocortisone 20 mg PO every AM, 10 mg PO every PM); it may also include levothyroxine for central hypothyroidism and testosterone supplementation in males. Patients may require physiologic replacement hormones indefinitely.

4.4.3.5 **Pulmonary Toxicity**

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension and the following should be performed:

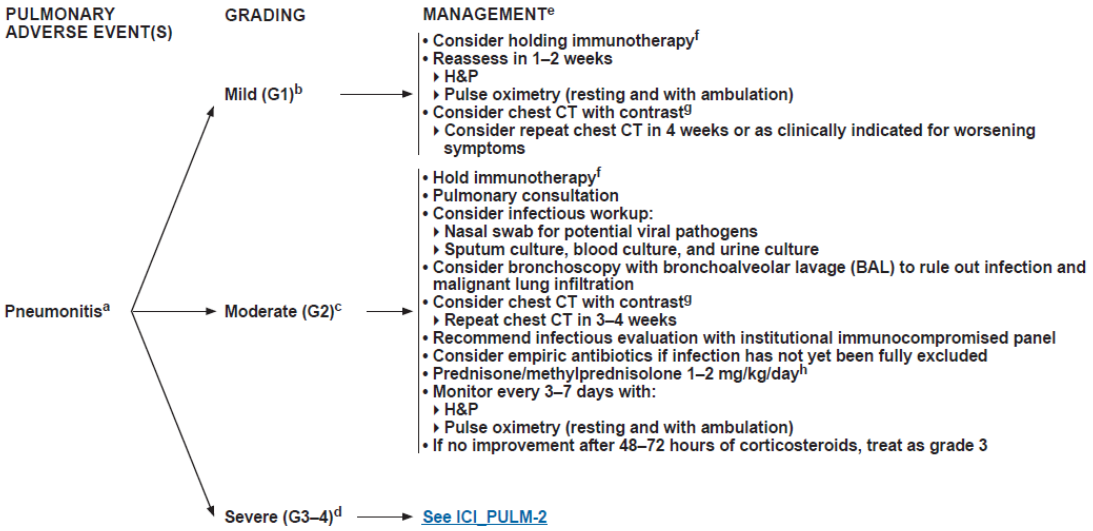
- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DL_{CO}])

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment (see Section 4.8.2).

Pulmonary toxicity may be managed according to guidelines and in Table 4.4.3.5. as well as per institutional standards.

Table 4.4.3.7Dose Interruption Guidelines for Pulmonary Toxicity

*Immunotherapy is atezolizumab



[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[c] Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement.
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] CT with contrast to rule out other etiologies if not contraindicated.
[h] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

Table 4.4.3.8 Dose Interruption Guidelines for Pulmonary Toxicity (cont.)

ASSESSMENT/ GRADING	MANAGEMENT[e]
Severe (G3–4)[d] pneumonitis[a]	• Permanently discontinue immunotherapy[f] • Inpatient care • Infectious workup: ‣ Consider that patient may be immunocompromised ‣ Nasal swab for potential viral pathogens ‣ Sputum culture, blood culture, and urine culture • Pulmonary and infectious disease consultation, consider PFTs • Bronchoscopy with BAL to rule out infection and malignant lung infiltration • Consider empiric antibiotics if infection has not yet been fully excluded • Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks • Consider adding any of the following if no improvement after 48 hours: ‣ Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider ‣ Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service ‣ Intravenous immunoglobulin (IVIG)[i]

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADL; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Total dosing should be 2 g/kg, administered in divided doses per package insert.

4.4.3.6 Potential Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup may include an evaluation for obstruction, as well as serum amylase and lipase tests (see also Section 4.4.3.4).

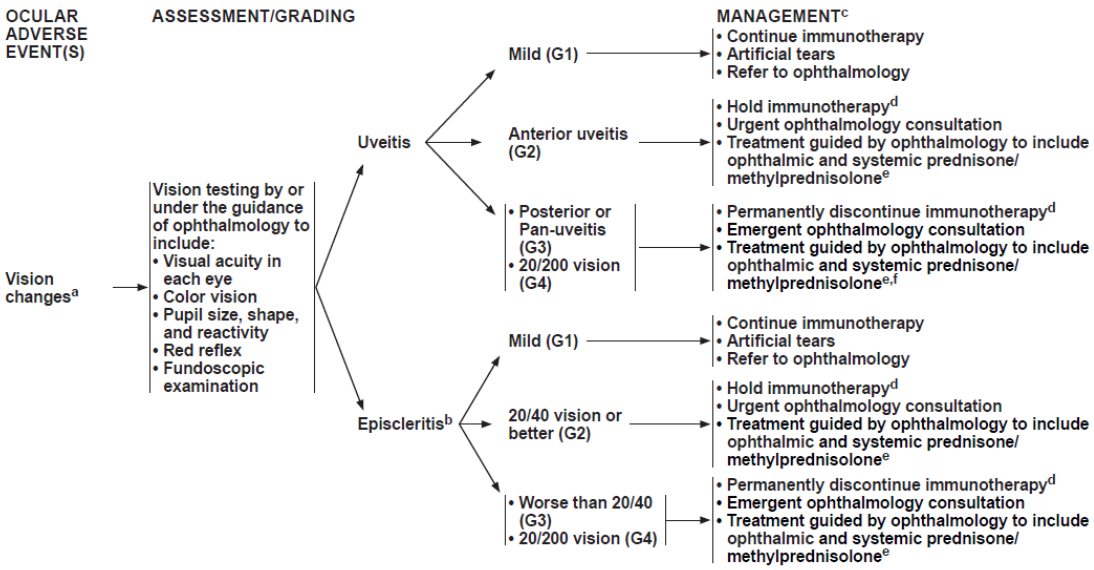
4.4.3.7 Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Ocular toxicity may be managed according to the guidelines in Table 4.4.3.7 as well as per institutional standards.

Table 4.4.3.7 Dose Interruption Guidelines for Eye Toxicity

*Immunotherapy is atezolizumab



[a] Patients experiencing ocular adverse events (AEs) may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, proptosis. Episcleritis can be associated with red or purple discoloration of the eye. Uveitis can be associated with eye redness.
[b] Treat blepharitis per the episcleritis algorithm.
[c] See Principles of Immunosuppression (IMMUNO-A).
[d] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[e] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[f] If refractory to high-dose systemic steroids, consider adding infliximab or antimetabolites (eg methotrexate) for pan-uveitis.

4.4.3.8 Potential Cardiac Toxicity

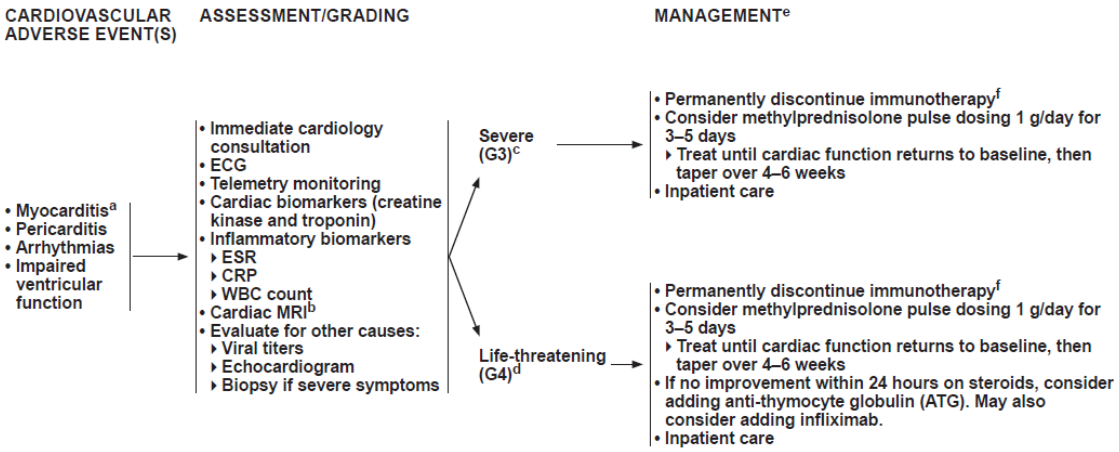
Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected if any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, may be treated according to the guidelines, and in Table 4.4.3.8 as well as per institutional standards.

Table 4.4.3.8 Dose Interruption Guidelines for Cardiac Toxicity

*Immunotherapy is atezolizumab



[a] Myocarditis symptoms are nonspecific. It is rare, but potentially severe, not viral in etiology, associated with myositis/myasthenia gravis, and is more common with combination therapy. In fatal cases, conduction abnormalities were mode of death and ejection fraction was preserved.
[b] No evidence specific to immunotherapy-related myocarditis; recommendations drawn from other causes of myocarditis.
[c] Arrhythmia, significant echo findings without hypotension, cardiac markers >ULN.
[d] Arrhythmia, hemodynamic (hypotension/cardiomyopathy) >3xULN.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).

4.4.3.9 Principles of Immunosuppression

Please see below for references to Principles of Immunosuppression as related to the management of toxicities.

PRINCIPLES OF IMMUNOSUPPRESSION

- These immunosuppression recommendations are for patients receiving immune checkpoint inhibitor immunotherapy.
- Close consultation with disease-specific subspecialties is encouraged.
  - Referral to a tertiary care center may be required for management of complex cases or multi-system irAEs.
- Corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy.
  - Early intervention with corticosteroids is a key goal in general management of immune-related toxicity.
  - Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor efficacy.
    - ◊ In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with corticosteroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis and hepatitis.
  - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the Principles of Immunotherapy Rechallenge (IMMUNO-C) for guidance by organ site.
  - Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 4 or more weeks.
  - Prophylaxis against fungal infections (eg, fluconazole) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 6–8 or more weeks.
  - Prophylaxis against herpes zoster reactivation can be considered.
  - Proton pump inhibitor therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of corticosteroid therapy.
  - Higher potency (eg, Class 2 or 3) topical corticosteroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
  - For neurologic, cardiac, or grade 3 or 4 irAEs, higher dose steroids (eg, methylprednisolone or prednisone 1–2 mg/kg/day) should be given.
  - If patients need to be on long-term steroids, they are at risk for developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis.
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for corticosteroid therapy. See Endocrine Toxicities section.

PRINCIPLES OF IMMUNOSUPPRESSION

- Anti-TNFα agents (eg, infliximab) are particularly effective in management of immune-related colitis and inflammatory arthritis.
  - There is a risk for hepatitis B virus reactivation with infliximab. Test for viral hepatitis B and hepatitis C prior to TNF inhibition and monitor HBV/HCV carriers during and for several months after therapy.
  - There is a risk for tuberculosis (TB) activation. Test for latent/active TB prior to TNF inhibition. TB testing should not delay initiation of anti-TNFα agents for the management of irAEs.
    - ◊ Results of TB testing need not be finalized prior to dosing anti-TNFα agents in the acute setting.
    - ◊ Interferon-gamma release assays for TB testing are preferred.
  - For patients with severe irAEs not responsive to steroids within 48–72 hours, early (~72 h) initiation of anti-TNFα therapy (eg, infliximab 5 mg/kg) may be warranted in consultation with the relevant medical specialist.
    - ◊ Close monitoring and follow-up of patients on steroids and infliximab is required to assess for response.
    - ◊ A second dose of anti-TNFα therapy may be required, and can be administered 2 weeks after initial dose of infliximab.
  - Anti-TNFα agents should be avoided in patients with immune-related hepatitis.
    - ◊ Alpha-4 beta-7 integrin inhibitors (eg, vedolizumab) may be considered in these cases for management of concomitant hepatitis and immune-related colitis.
    - ◊ Other immunosuppressive agents may be of use in certain irAEs; see individual toxicity pages.
- Patients with pre-existing autoimmune conditions or organ transplant recipients may be candidates for immune checkpoint blockade.
  - Anti-CTLA-4–based therapy has a higher incidence of exacerbating baseline autoimmune conditions relative to anti-PD-1/PD-L1–based approaches.
  - Optimization of immunosuppression for pre-existing autoimmune conditions, including close follow-up with pertinent subspecialists, is recommended.
    - ◊ Goal of immunosuppressive regimen allowing for dose of prednisone <10 mg daily or equivalent prior to initiating cancer immunotherapy.
  - Graft failure while on cancer immunotherapy has been reported. Transplant organ loss may be an outcome of treatment with cancer immunotherapy and should be discussed with patient and organ transplant team.
    - ◊ Patients with solid organ transplantation who have viable option for alternative therapy if graft rejection (eg, kidney) may be candidates for immunotherapy, particularly if no prior evidence of graft rejection and if on maintenance immunosuppression.
  - Patients with autoimmune neurologic conditions or life-threatening autoimmune disorders, particularly if not controlled with immunosuppressive medications or requiring high doses of immunosuppression, are unlikely to be suitable candidates for cancer immunotherapy.
  - Patients with prior allogeneic stem cell transplant may be candidates for immunotherapy.
    - ◊ There is an increased risk of transplant-related complications, including potentially fatal graft-versus-host disease (GVHD).
    - ◊ Careful discussion with patient and stem cell transplant physicians should precede initiation of immunotherapy.
- Patients with history of HIV or viral hepatitis may be candidates for immunotherapy.
- Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.

4.4.3.10 **Principles of Immunotherapy Rechallenge**

Please see below for references to Principles of Immunotherapy Rechallenge as related to the management of toxicities.

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

General Principles

- Exercise caution when considering resumption of immunotherapy after significant irAEs. Close follow-up should be performed when resuming immunotherapy to monitor for recurrent symptoms.
  - If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.
  - Assess patient's tumor status prior to rechallenge. If an objective response (complete or partial) to ICI therapy was achieved, resumption of immunotherapy may not be advisable due to risk of toxicity recurrence. Discuss the risks/benefits of restarting immunotherapy with the patient.
- Permanent discontinuation of a given class of immunotherapy is typically warranted in the setting of severe irAEs induced by that class of immunotherapy and may be warranted in the setting of moderate irAEs. For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with a PD-1 or PD-L1 monotherapy after resolution of the earlier toxicity.
- With some exceptions, resumption of immunotherapy following grade 2 irAEs can be considered upon resolution to ≤ grade 1.
- Consult with organ-specific specialists prior to resumption of immunotherapy as appropriate following an immunotherapy hold due to irAEs.

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Skin	• Maculopapular rash and/or pruritus: Consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.
GI	• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg prednisone equivalent daily. • CTLA-4 agents: Discontinue if irAE is serious or life-threatening. Do not make up doses missed due to irAE and/or required steroid treatment.
Liver	• Transaminitis without elevated bilirubin: following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 3–4) hepatitis.
Pancreas	• Symptomatic grade 2 pancreatitis: Consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreatic specialist regarding resumption. • Permanent discontinuation is warranted for severe (grade 3–4) pancreatitis.

PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Endocrine	• Thyroid: No discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Primary adrenal insufficiency: After appropriate replacement endocrine therapy is instituted, immunotherapy may continue. • Hypophysitis manifested by deficiency of TSH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: Immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): Hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms related to mass effect are resolved. • T1DM with DKA: Consider resuming once DKA has been corrected and glucose level has stabilized.
Lung	• Progressive grade 1 pneumonitis requiring a hold: Consider resuming upon radiographic evidence of improvement. • Grade 2: Resume once pneumonitis has resolved to ≤ grade 1 and patient is off steroids. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) pneumonitis.
Kidney	• Grade 1–2 renal irAE: Hold immunotherapy per guidelines; upon resolution to ≤ grade 1, consider resuming concomitant with steroid if creatinine is stable. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) proteinuria.
Eye	• Grade 2 irAE: Hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology upon resolution to ≤ grade 1. • Permanent discontinuation of immunotherapy is warranted in the setting of severe (grade 3–4) uveitis or episcleritis.
Nervous System	• Myasthenia gravis: Consider resuming immunotherapy after moderate (grade 2) AE based on steroid responsiveness. Permanently discontinue immunotherapy after grade 3–4 AE. • GBS: Permanently discontinue immunotherapy for any grade GBS. • Peripheral neuropathy: Following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: Consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: Permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4). • Transverse myelitis: Discontinuation of immunotherapy following any-grade transverse myelitis.
Cardiovascular	• Grade 1 myocarditis: Consider resuming upon resolution of symptoms. • Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): Resume upon stabilization or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.

4.4.4 Guidelines for Interval Cytoreduction Surgery Modification

4.4.4.1 In the event a patient is unable to get surgery after cycle 3 due to medical issues, the patient may still continue on study at the discretion of the treating physician and the Duke PI.

4.4.4.2 In the event a patient needs to have interval cytoreductive surgery earlier than the scheduled timeframe due to medical issues, the patient may have the surgery earlier and continue on study at the discretion of the treating physician and the Duke PI.

4.4.4.3 For patients with modified ICS timelines, optional bevacizumab timing will differ. Bevacizumab should not be given the cycle prior and the cycle after ICS. Timing of bevacizumab administration will be at the discretion of the treating physician.

4.5 PATIENT DISCONTINUATION

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with protocol or treatment

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate Case Report Form (CRF). However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

See Section 4.8.2 and Section 4.8.3 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

4.6 STUDY TREATMENT DISCONTINUATION

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Immune-related toxicities as outlined in Section 4.4.3
- Intercurrent illness, which in the judgment of the investigator, affects assessments of clinical status to a significant degree or requires discontinuation of study treatment
- Non-protocol anti-cancer therapy (including but not limited to chemotherapy, hormonal therapy, or immunotherapy) administered during study treatment (refer to Section 4.3)
- Wish to discontinue treatment.

The primary reason for study treatment discontinuation should be documented on the appropriate CRF. Patients who discontinue study treatment prematurely will not be replaced. Patients who discontinue for toxicity or choice can continue to be followed per protocol to assess study objectives.

4.7 STUDY AND SITE DISCONTINUATION

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

4.8 CLINICAL AND LABORATORY EVALUATIONS

4.8.1 Pretreatment Evaluations

Written documentation of full, unconditional IRB approval of the protocol and consent document must be on file before a patient can be screened. Patients will be assigned a study identification number upon signing consent.

The following pretreatment evaluations must be performed within 4 weeks of initiation of study treatment:

1. Signed patient informed consent
2. Medical history
3. Physical exam, including height, weight, and vital signs
4. Serum pregnancy test, if applicable
5. Baseline imaging (CT or MRI)
6. Laparoscopic excisional or image-guided core biopsy to confirm diagnosis and obtain research specimens

The following pretreatment evaluations must be performed within 14 days of initiation of study treatment:

7. Laboratory evaluations including: CBC with auto differential, CMP, CA125, TSH, magnesium, phosphorus.

4.8.2 Study Assessments

The flowchart of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.8.2.1 **Medical History**

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), prior cancer therapies and procedures, and all medications used by the patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

4.8.2.2 **Vital Signs**

Vital signs may include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures, and temperature.

Vital signs should be collected during the infusion per institutional standard and as clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

4.8.2.3 **Physical Examination**

A complete physical examination will be performed at screening and at the treatment discontinuation visit and may include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

As part of tumor assessments, a physical examination will be performed.

All patients should be monitored for symptoms of brain metastases. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological examination. A CT or magnetic resonance imaging (MRI) scan of the head should be done as clinically indicated to confirm or refute new or worsening brain involvement.

If the screening exam is performed within 3 days of day#1 of cycle #1, the exam does not need to be performed again.

4.8.2.4 **Tumor and Response Evaluation**

Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. For solid malignancy patients with measurable disease, response will be assessed by the investigator per RECIST v1.1 (see Appendix 4) and immune-related response criteria (irRC; see Appendix 5).

Imaging (CT or MRI) will be performed as follows:

1. during the screening period, to document measurable disease

2. after 3 cycles of chemotherapy with atezolizumab (prior to ICS) to assess response and suitability for ICS,

3. after completion of 6 cycles of chemotherapy with atezolizumab to assess response at end of chemotherapy treatment,

4. as clinically indicated during the maintenance therapy with atezolizumab alone and after completion of study treatment (to assess PFS).

4.8.2.5 **Laboratory Assessments**

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. See Study Flowchart for timing of laboratory assessments (Appendix 1).

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin)
- CA-125
- Coagulation (aPTT and INR)
- Pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) if/when indicated
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (TSH and free T4, if TSH is elevated), hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated
    - HBV DNA test is required for patients who have known positive serology for anti-HBc
    - HCV RNA test is required for patients who have known positive serology for anti-HCV

Refer to Section 9 and the laboratory manual for additional details on translational laboratory assessments and sample handling.

4.8.3 Treatment Discontinuation Visit and Safety Follow-up

Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients will be followed for safety for 90 days following the last dose of atezolizumab or until receipt of another anticancer therapy, whichever comes first.

4.8.4 Follow-Up Assessments

If the maintenance atezolizumab is completed or discontinued before disease recurrence, the patient will be followed for recurrence according to NCCN guidelines [11]. Specifically, patients should be evaluated with physical exam at routine intervals and if there is concern for clinical relapse or serially rising CA125, imaging studies as clinically indicated should be obtained. Disease assessments will be recorded on the patient CRF until treatment with another anticancer therapy for recurrence is initiated.

4.8.5 Long-Term Follow-up

After disease recurrence, survival data will be collected every 6 months (+/- 1 month) from the treating physician, research coordinator, public records, or by direct contact with the patient by the investigator for a maximum of 5 years from Cycle 1 Day 1. Information about further treatments for ovarian cancer will also be collected as possible by the investigator.

5. STATISTICAL ANALYSES

5.1 DEFINITIONS

Progression Free Survival: All patients will be evaluated for progression free survival from the date of first treatment to the date of first observation of progressive disease or death due to any cause or will be censored at date of last follow-up for those still alive without disease progression.

Overall Survival: All patients will be evaluated for overall survival from the date of first treatment on protocol to the date of death due to any cause and will be censored at date of last follow-up for those still alive.

Sample Size: It is estimated that 40 patients will be enrolled at an accrual rate of 3-5 patients/month and followed for a median of 3 years

5.2 STUDY DESIGN/STOPPING RULE

This study is a phase Ib trial with the endpoint of validating the safety of the combination of atezolizumab in combination with weekly dose-dense paclitaxel

and carboplatin for treatment of ovarian cancer in the neoadjuvant setting. The primary adverse event of interest is the inability of patients to proceed to planned ICS within the specified timeframe (⩽6 weeks from last dose of NACT) as a result of atezolizumab-related toxicities. With NACT, approximately 12% of patients are unable to proceed to surgery due to lack of response or comorbidities [21]. Thus, there is a ⩾ 90% chance that ⩽ 2 patients out of 10 would be unable to proceed to surgery and a ⩾ 90% chance that ⩽ 5 patients out of 25 would be unable to proceed to surgery. Thus, we have set the following as stopping rules for the study combination:

- If there are 3 or more patients out of the first 10 patients who are unable to proceed to surgery within the expected timeframe due to adverse events, enrollment will be paused. The chance of stopping the trial is less than 10% if the combination causes fewer patients to be unable to proceed to surgery than standard care. Under this stopping rule, the chance of stopping the trial is 44% if true rate of patients who are unable to proceed to surgery is 24%;
- If there are 6 or more patients, out of the first 25 patients evaluable in the safety population, unable to proceed to surgery within the expected time frame due to adverse events, enrollment will be paused. The chance for stopping the trial is less than 10% if the combination causes fewer patients to be unable to proceed to surgery than standard care. Under this stopping rule, the chance of stopping the trial is 58% even if true rate of patients who are unable to proceed to surgery is 24%.

In the event of unacceptable atezolizumab-related toxicity that interferes with performance of ICS, an amendment to the dose and/or schedule of chemotherapy will be considered to improve tolerability, and the new dose/schedule will be evaluated according to the same decision rules. We will provide an estimate of the proportion unable to go to surgery and its 95% binomial exact confidence interval.

5.3 POPULATIONS

5.3.1 Safety Population

Data from all subjects who receive any protocol therapy will be included in the safety analyses. Subjects who entered the study and did not receive any protocol therapy, and had this confirmed, will not be evaluated for safety.

5.3.2 Pharmacodynamic/Translational Population

The pharmacodynamic/translational population will consist of all subjects with any evaluable translational study results (including PD-L1 expression, tumor-infiltrating lymphocyte subpopulations, immune checkpoint receptor profiles, gene expression profiles associated with immunoactivation, cytokine expression profiles, *BRCA* mutation status, tumor mutation profiles, and angiogenic markers.

5.3.3 Efficacy Evaluable Population

The efficacy population will include all subjects who receive at least 1 dose of study drug. Patients without a post-dose efficacy assessment will be considered non-responders for response analysis. All progression of disease or death during follow-up period will be included as events for PFS and OS analysis.

5.4 STATISTICAL METHODOLOGY

5.4.1 Safety Analyses

Safety evaluation will include physical examinations, vital sign measurements, laboratory assessments, and monitoring for adverse events. The severity of toxicities will be graded according to the NCI CTCAE v5.0, whenever possible. Adverse events and clinically significant laboratory abnormalities (meeting Grade 3-5 criteria according to CTCAE) will be summarized by maximum intensity and relationship to study drug. Simple descriptive statistics will be utilized to display the data on toxicity observed from the combination of atezolizumab with weekly dose-dense paclitaxel and carboplatin.

5.4.2 Efficacy Analyses

All efficacy endpoints will be summarized descriptively using frequency distributions. In addition, 95% confidence intervals will be provided for the proportion of each response. PFS and OS will be determined using the Kaplan-Meier method. Median and 2-year survivals will be estimated along with 95% confidence intervals.

5.4.3 Translational Analyses

5.4.3.1 Correlation of PD-L1 expression to clinical outcomes

Expression of PD-L1 will be correlated with clinical outcomes. Efficacy analyses will be repeated based on PD-L1 expression levels. The population will be divided into two categories of high versus low expression based on IHC staining. The cut-point will be determined with input from the Genentech development team.

5.4.3.2 Other translational endpoints

The other translational endpoints are exploratory and hypothesis generating. They will be summarized with descriptive statistics and correlated to the clinical outcomes of interest.

5.5 SAMPLE SIZE

The sample size for the study was primarily determined based on feasibility of accrual and level of support. However, the sample size is sufficient to determine the safety and primary translational endpoints as outlined above.

6. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to atezolizumab, all events of death, and any study-specific issue of concern.

6.1 RISKS ASSOCIATED WITH ATEZOLIZUMAB

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related AEs, specifically the induction or enhancement of autoimmune conditions. AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, myositis, and myasthenia gravis, have been observed in Study PCD4989g.

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications [22].

A more detailed safety profile of atezolizumab is provided in the atezolizumab Investigator's Brochure.

6.2 SAFETY PARAMETERS AND DEFINITIONS

6.2.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms of ovarian cancer that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

6.2.2 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death)

- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

6.3 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate Institutional Review Boards (IRBs), and Genentech, Inc., in accordance with CFR 312.32 (Investigational New Drug [Nixon, #24] Safety Reports).

6.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of any study procedures and ends 90 days following the last administration of study treatment or until receipt of another anticancer therapy, whichever comes first. After this period, investigators should only report SAEs that are attributed to prior study treatment.

6.3.2 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to atezolizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab, and the AE cannot be readily explained by

the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab; and/or the AE abates or resolves upon discontinuation of atezolizumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than atezolizumab (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

6.4 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

6.4.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

6.4.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

6.4.2.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

6.4.2.2 **Deaths**

All deaths that occur during the protocol-specified AE reporting period (see Section 6.3.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

6.4.2.3 **Pre-existing Medical Conditions**

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

6.4.2.4 **Hospitalizations for Medical or Surgical Procedures**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

6.4.2.5 **Pregnancies in Female Patients**

If a female subject becomes pregnant while receiving atezolizumab or within 5 months after the last dose of atezolizumab, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to atezolizumab should be reported as an SAE.

6.4.2.6 **Post-Study Adverse Events**

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior atezolizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

6.4.2.7 **Safety Reconciliation**

The Sponsor-investigator agrees to conduct reconciliation for the product. Genentech and the Sponsor-investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor-investigator and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech/Roche shall be forwarded by the Sponsor to Genentech/Roche within five (5) calendar days from request by Genentech/Roche.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech/Roche

6.4.2.8 **Adverse Events of Special Interest**

Adverse events of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP.

The following AEs are considered of special interest and must be reported to the Genentech Drug Safety expeditiously (see Section 6.4.2.9 for reporting instructions), irrespective of regulatory seriousness criteria:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
    - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study treatment, as defined below
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Atezolizumab Adverse Events of Special Interest are:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism or adrenal insufficiency, hypophysitis
- Hepatitis
- Transaminitis: Grade $\geq$ 2 (AST or ALT $>$ 3 $\times$ ULN and bilirubin $>$ 2 $\times$ ULN) or AST/ALT $>$ 10 $\times$ ULN
- Systemic lupus erythematosus
- Guillain-Barré syndrome
- Myasthenia gravis or myasthenic syndrome
- Meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation or infusion-reaction syndromes
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geqslant$ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

6.4.2.9 **Adverse Event Reporting**

Investigators must report all significant AEs as identified below to the Duke Cancer Institute Safety Surveillance Office, who will report on behalf of the study to Genentech within the timelines described below.

Contact for AE reporting:

Duke Cancer Institute Safety Surveillance Office:
Fax: (919) 681-9357, Phone: (919) 681-9538,
Email: dcccsafe@dm.duke.edu

Relevant follow-up information should be submitted to Genentech Drug Safety by the Duke Safety Surveillance Office as soon as it becomes available.

- Serious adverse events (SAEs), pregnancy reports and AEs of special interest (AESIs), where the patient has been exposed to the atezolizumab, will be sent on a MedWatch form to Genentech/Roche by the Duke Safety Surveillance Office. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:
  SADRs: Serious AE reports that are related to the Product shall be transmitted to Genentech/Roche by the Duke Safety Surveillance Office within fifteen (15) calendar days of the awareness date.

- **Other SAEs:** Serious AE reports that are unrelated to the Product shall be transmitted to Genentech /Roche by the Duke Safety Surveillance Office within thirty (30) calendar days of the awareness date.

- **AESIs:** AESIs shall be forwarded to Genentech/Roche by the Duke Safety Surveillance Office within fifteen (15) calendar days of the awareness date.

- **Pregnancy reports:** While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech/Roche by the Duke Safety Surveillance Office within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech/Roche by the Duke Safety Surveillance Office even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Aggregate Reports

Dr. Secord will forward a copy of the Final Study Report to Roche upon completion of the Study or will forward periodically listings of non-serious AEs originating from the Study to Roche or will forward a copy of the Publication to Roche upon completion of the Study.

The Sponsor- Investigator of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. The Sponsor- Investigator agrees to share a copy of their own DSUR with Genentech/Roche as soon as reasonably possible after completion. Genentech/Roche agrees to forward to the Sponsor- Investigator an executive summary of the Genentech/Roche DSUR upon request. Furthermore, Genentech/Roche agrees that the Sponsor-Investigator may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

6.4.3 Additional Reporting Requirements for IND

Study is IND exempt. Not applicable.

6.4.4 IND Annual Reports

Not Applicable

6.5 STUDY CLOSE-OUT

Any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Atezolizumab Protocols

Email: anti-pdl-1-mpd3280a-gsur@gene.com, noska.april@gene.com and ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by the Sponsor-Investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall

have the final say and control over safety queries relating to the Product. The Sponsor - Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. The Sponsor Investigator agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

7. ETHICAL CONSIDERATIONS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive atezolizumab treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, completion of planned protocol treatment, or any of the other reasons for treatment discontinuation listed in Section 4.4.4.

7.2 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be

provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

7.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

7.4 CONFIDENTIALITY

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

8. STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI, institutionally by the Duke Cancer Institute (DCI), and externally by the IRBs at Duke University Medical Center and participating sites. External site monitoring will be performed in accordance with the **External Site Monitoring Plan**, which accompanies this protocol. Please refer to this document for specifics regarding monitoring procedures. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the IRBs at Duke University Medical Center and additional sites will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual,

outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

8.1 STUDY MEDICATION ACCOUNTABILITY

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

8.2 DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the local IRB.

8.3 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

9. TRANSLATIONAL STUDIES

9.1 BIOLOGIC SAMPLES FOR BIOMARKER AND CORRELATIVE STUDIES

During the course of this trial, biologic samples will be collected at two time points for biomarker and correlative studies, including immunohistochemistry, RNAseq, immune checkpoint profiling, and cytokine expression profiling. Please refer to the laboratory manual for details on specimen requirements, collection time points, and shipping instructions.

9.2 BRCA MUTATION STATUS

BRCA germline mutation status will be collected when available at baseline, or when it becomes available during study participation. If results are not available, testing will not be mandated.

Patients with germline or somatic BRCA mutations may continue on study or discontinue to receive a PARP inhibitor at their discretion and after discussing with their primary treating care provider.

9.3 TUMOR MUTATION PROFILE

Tumor mutation profile information will be collected if it becomes available during study participation. If results are not available, testing will not be mandated.

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Appendix 1 Study Flowchart

Day	Screening		Treatment Period								Study Completion/Early Term Visit	Follow-Up	Long-term follow-up
	-28 to -1	-14 to -1	C1-3 D1	C1-3 D8	C1-3 D15	ICS[14]	C4-6 D1	C4-6 D8	C4-6 D15	Maintenance Atezolizumab D1	≤30 days after last treatment	per NCCN guidelines until recurrence	every 6 months
Window			+/-3	+/- 1	+/-1	Within 42 days from C3D1	+/- 3	+/-1	+/-1	+/-3			+/- 1 month
Informed consent	X												
Demographic data	X												
General med history & baseline conditions	X												
Vital signs [1]	X		X				X			X	X		
Weight & height [7]	X		X				X			X	X		
Physical examination[12]	X		X				X			X	X		
Concomitant medications		X	X				X			X	X		
Hematology [2]		X	X[11]	X	X		X	X	X	X	X		
Chemistry [3]		X	X[11]				X			X	X		
Coagulation studies[4]		X											
CA125		X	X[9, 11]				X			X	X	X	
TSH		X	X[11]				X			X	X		
Serum pregnancy test	X[10]		X[10]			X[10]							
Hepatitis serology[6]	X												
Urinalysis	X												
Baseline imaging/response assessment[5]	X					X				X		X	
Translational Studies Specimens [8]	X	X				X							
Atezolizumab administration			X				X			X			
Carboplatin administration			X				X						
Paclitaxel Administration			X	X	X		X	X	X				
Bevacizumab Administration (Optional)[13]							X[13]			X			
Recurrence and Survival data													X

[1] Heart rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
[2] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
[3] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, magnesium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus.
[4] INR and aPTT
[5] imaging of the chest, abdomen, and pelvis by CT or MRI, the same modality that was used for baseline imaging should be used for response assessment. Imaging at ICS is to be performed prior to surgery. Imaging is to be performed after completion of chemotherapy and then as clinically indicated during maintenance and follow-up periods.
[6] hepatitis serologies as clinically indicated, especially in high risk patients
[7] height should be obtained prior to C1D1, subsequent measurements as clinically indicated
[8] See Section 9 and laboratory manual for information regarding translational studies specimens. During the screening period, the pretreatment tumor sample and pretreatment research blood sample may be collected up to 28 days prior to cycle 1 day1 of therapy. For pre-treatment biopsy, only upon agreement of the Investigator an alternative sample should be provided as per inclusion criteria section 4.1.1 prior to initiation of study treatment, these cases may omit the need to biopsy for newly obtained pre-treatment specimen. The ICS research blood sample may be collected up to 14 days before ICS if not feasible on the day of surgery.
.[9] Only for cycles 2 and 3
[10] Pregnancy test not required for women of non-childbearing potential
[11] Screening labs may be used if collected within 7 days of C1D1
[12] Physical exam does not need to be repeated on D1 of C1 if performed within the last 3 days.
[13] Optional Bevacizumab can be given starting at cycles 5 and 6 of adjuvant chemotherapy and throughout maintenance. For patients with ICS delayed or ICS performed earlier, bevacizumab timing will differ. Bevacizumab should not be given at the cycle prior and cycle after ICS. Timing of bevacizumab administration will be at the discretion of the treating physician.
[14] Patients who have medical issues that may need to delay or have ICS performed earlier may still continue on study at the discretion of the treating physician and the Duke PI

Appendix 2 Initial Carboplatin Dose Recommendations based on IDMS Creatinine Values

Initial Carboplatin Dose Recommendations based on IDMS Creatinine Values (based on NCI and legacy GOG recommendations)*

Calculate using Calvert formula**	$\text{Carboplatin Total Dose (mg)} = \text{Target AUC (mg} \cdot \text{min/mL)} \cdot [\text{GFR} + 25]\ \text{(mL/min)}$
Estimate GFR using Cockcroft-Gault equation***	$\text{Creatinine Clearance (mL / min)} = \frac{[140 - \text{Age (years)}] \cdot \text{Weight (kg)} \cdot 0.85\ \text{(for women)}]}{72 \cdot \text{Serum Creatinine (mg / dL)}}$
Body Weight: For body mass index (BMI) <25, use actual body weight For BMI >25****, use adjusted body weight	$\text{Adjusted Weight (kg)} = (\text{Actual Weight} - \text{Ideal Weight}) \cdot 0.40) + \text{Ideal Weight})$ $\text{Ideal Weight (kg)} = ([\text{Height in cm}/2.54] - 60) \cdot 2.3) + 45.5$
For abnormally low serum creatinine values, GFR should be capped at a maximum value of 125 mL/min or estimated GFR can be calculated using the lower limit of normal for the serum creatinine test utilized (frequently set at 0.7mg/dL).	**Maximum Carboplatin Dose:** AUC 6 = 900mg AUC 5 = 750 AUC 4 = 600

*Subsequent modifications are based on hematologic toxicity or recalculation in the event of a change in renal function or body weight.

**Although developed with measured GFR, estimated GFR is routinely employed in clinical practice

***Of note, although the Cockcroft-Gault equation was developed and validated for drug dosing using pre-IDMS creatinine values, it is the preferred formula for estimating GFR.

****The BMI cut-off for using adjusted body weight is under review, revised guidelines with a higher cut-off are expected.

Reference:

Ivy SP, Zwiebel J, Mooney M. Follow-up for Information Letter Regarding AUC-Based Dosing of Carboplatin. Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute. http://ctep.cancer.gov/content/docs/Carboplatin_Information_Letter.pdf. Accessed December 10, 2015.

Appendix 3 Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST)

Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

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

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When 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.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis $<$ 10 mm are considered non-pathological and should not be recorded or followed.

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 of diameters. If lymph nodes are to be included in the sum, then, as noted

above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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 diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual

measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the time points specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response.

For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

Evaluation of Response

a. Time point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1. Time point Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2. Time point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that time point.

Table 3. Best Overall Response When Confirmation Is Required

Overall Response at First Time point	Overall Response at Subsequent Time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of “zero” on the CRF.

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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such

patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 – 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5 Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_{i} \text{(Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i)}.$$

[1] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden $\geq 50\%$ relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden $\geq 25\%$ relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 6 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

Appendix 7 Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.

Appendix 8 Safety Reporting Fax Cover Sheet

Send to Duke Safety Surveillance Office:

Email: dcccsafe@dm.duke.edu, Fax: (919) 681-9357, Phone: (919) 681-9538

Genentech
A Member of the Roche Group

GENENTECH SUPPORTED RESEARCH

AE/SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-4630

Page 1 of ___

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/_____/_____ dd / mmm / yyyy
Follow-up Report Date	_____/_____/_____ dd / mmm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	____ - ____ -____

SAE or Safety Reporting questions, contact Duke Cancer Institute Safety Surveillance Office: Fax: (919) 681-9357, Phone: (919) 681-9538

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

Appendix 9 FDA MedWatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email.

Appendix 10 Eligibility Checklist

Study #: Pro00079313	Subject ID #:			
Inclusion Criteria	**Yes**	**No**	**N/A**	**Site Coordinator Confirmation (Initial/Date)**
Patient is willing and able to provide written informed consent for the trial				
Patient has ability and willingness to comply with the requirements of the study protocol				
Patient is ≥ 18 years of age on day of signing informed consent				
Patient has no history of prior treatment for primary advanced (stage III or IV) epithelial ovarian, fallopian tube, or primary peritoneal carcinoma				
Patient has confirmation of diagnosis and patients for whom the plan of management will include NACT followed by ICS. The decision to proceed with NACT will be at the treating physician's discretion and include patients with advanced stage disease considered at a low likelihood for optimal cytoreduction with primary debulking surgery				
Patient has measurable disease per RECIST v1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one direction (longest diameter recorded). Each lesion must be ≥ 10mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20mm when measured by chest x-ray. Lymph nodes must be ≥ 15mm in short axis when measured by CT or MRI				
Patient has histology consistent with high-grade epithelial ovarian cancer				
Patient has an adequate pre-treatment tumor biopsy. Includes laparoscopic biopsy or image-guided core needle biopsy (minimum of two cores). Fine needle aspiration (FNA) biopsy or cytology form ascites may be adequate at the discretion of the investigator. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement of the investigator. *****Sponsor approval required for FNA, archival, or cytology specimens*****				
Patient has adequate hematologic and end organ function within 14 days prior to first study treatment (Cycle 1, Day 1): • **Absolute Neutrophil Count** ≥ 1,500/mcl • **Lymphocyte Count** ≥ 300/mcl • **Platelets** ≥ 100,000/mcl. • **Hemoglobin** ≥ 9.0 g/dL • **Bilirubin** ⩽ 1.5 X ULN If patient has known Gilbert disease who have serum bilirubin level ≤ 3 ULN may be enrolled • **AST & ALT** ≤ 3.0 X ULN If patient has liver involvement: AST & ALT ≤ 5 X ULN • **Alkaline phosphatase** ≤ 2.5 X ULN. If patient has documented liver involvement or bone metastases: alkaline phosphatase ≤ 5 X ULN. Isolated alkaline phosphatase ≤ 5 X ULN with normal AST, ALT, and bilirubin is acceptable based on investigator discretion. • **Creatinine Clearance** ≥ 50 mL/min • **International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)** ≤1.5 X ULN unless subject is receiving anticoagulant therapy; patients receiving therapeutic anticoagulation should be on stable dose				
Patient has ECOG Performance Status of 0, 1 or 2				
Patient has peripheral neuropathy less than or equal to CTCAE Grade 1				
If patient is of childbearing potential: should be willing to use highly effective form(s) of contraception and to continue its use at least until ICS or if ICS if not performed then 90 days post last dose of atezolizumab. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year				
Patients who opt to receive bevacizumab must meet standard institutional treatment guidelines				

Study #: Pro00079313	Subject ID #:			
Exclusion Criteria	**Yes**	**No**	**N/A**	**Site Coordinator Confirmation (Initial/Date)**
Patient has mucinous, low-grade histology, or clear cell carcinoma				
Patient has prior systemic chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer				
Patient has prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years. Exceptions include basal cell or squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy				
Patient has AEs from prior anticancer therapy that have not resolved to Grade ≤ 1 except for alopecia				
Patient uses bisphosphonate therapy for symptomatic hypercalcemia. Use of biophosphonate therapy for other reasons allowed (e.g. bone metastasis or osteoporosis)				
Patient has known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease				
Patient has known primary central nervous system (CNS) malignancy or symptomatic CNS metastases				
Patient is pregnant or breastfeeding				
Patient has known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies				
Patient is unable to comply with study and follow-up procedures				
Patient has a history or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis • Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement therapy hormone may be eligible • Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible • Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided they meet the following conditions - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations manifestations - Rash must cover less than 10% of the body surface area (BSA) - Disease is well controlled at baseline and only requiring low potency topical steroid (e.g. hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%) hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%) - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids))				
Patient has a history of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), organizing pneumonia (i.e. bronchiolitis obliterans, crytogenic organizing pneumonia, etc.) or evidence of active pneumonitis on screening CT scan • Patients with history of radiation pneumonitis in the radiation field (fibrosis) are permitted				
Patient has any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an				

investigational drug or that may affect the interpretation of results or render the patient at high risk of treatment complications				

Study #: Pro00079313 **Subject ID #:**

Exclusion Criteria	**Yes**	**No**	**N/A**	**Site Coordinator Confirmation (Initial/Date)**
Patient has history of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection • Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible • Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA				
Patient has active tuberculosis				
Patient has severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia				
Patient has signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1				
Patient has received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1 • Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible				
Patient has received a live vaccine within 4 weeks of Cycle 1, Day 1 or anticipation of such a live, attenuated vaccine will be required during the study • Note: Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., Flu-Mist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study				
Patient has prior history of treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA4 or any other antibodies targeting co-stimulation or checkpoint pathways				
Patient has treatment with systemic immunostimulatory agents (including but not limited to interferon [Disis, #15]-α or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1				
Patient has treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)				
Patient has treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1 • Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled • The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed				
Patient has history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins				
Patient has had prior allogeneic bone marrow transplantation or prior solid organ transplantation				

_____ _____

Signature of Coordinator/Research Nurse **Date**

_____ _____

Signature of Investigator **Date**

Appendix 11 Registration Form

Subject Registration Form

Directions

Please scan/email the following documents for review to clinresearchgynonc@dm.duke.edu

- ☐ Completed and signed Eligibility Checklist
- ☐ Signed patient informed consent (signature page only—redact except for initials)
- ☐ Baseline CT, MRI, or Chest x-ray
- ☐ Pathology report
- ☐ Baseline hematology, chemistry, coagulation, TSH, and UA
- ☐ Most recent progress note (include current medication list, past medical history, and ECOG PS)
- ☐ Serum HCG (☐ Not Applicable)
- ☐ Baseline CA-125
- ☐ Any other applicable tests results (e.g. Hepatitis)

Eligibility will be confirmed via e-mail. Please allow 2-3 business days for return

Any Questions?

Please call (919) 684-3780
or email
clinresearchgynonc@duke.edu

Version 10Oct2018

Subject Registration Form

Section 1: SUBJECT INFORMATION

Subject Initials: _____ ____ _____ Date of Birth: ____/____/_____

Protocol Name: _____ Type of Cancer Diagnosis: _____

Date Consent Signed: ____/____/_____ Version Date of Site Consent: ____/____/_____

RACE:	ETHNICITY:
☐ White	☐ Hispanic or Latino
☐ Black or African American	☐ Non Hispanic or Latino
☐ Native Hawaiian or other Pacific Islander	☐ Not Reported
☐ Asian	☐ Unknown
☐ American Indian or Alaska Native	
☐ Not Reported	
☐ Unknown	

Section 2: SITE INFORMATION

Site Name: _____

Study Coordinator Name: _____ Phone #: _____

Study Coordinator Email: _____

Treating MD Name: _____ Phone #: _____

Treating MD Email: _____

Section 3: ELIGIBILITY

☐ Subject meets all eligibility criteria. *(Please note: If subject meets all eligibility criteria, please provide completed eligibility checklist along with supporting source documentation to the Duke team.)*

Date of expected Cycle 1 Day 1: ____/____/_____

☐ Subject does not meet all eligibility criteria. If subject does not meet eligibility, please explain below.

_____

Study Coordinator Signature: _____ Date: _____

Section 4: TO BE COMPLETED BY DUKE STUDY TEAM

Subject Study Number	
PI Signature or attach email confirmation	

Date Registration Form Received		Signature	
Date Registration Entered		Signature	
Date Site Notified of Eligibility		Signature	

Version10Oct2018

Appendix 12 Investigator Signature Page

Investigator Signature Page

Product: Atezolizumab

Protocol: Atezolizumab in Combination with Neoadjuvant Chemotherapy and Interval Cytoreductive Surgery for Patients with Newly-Diagnosed Advanced-Stage Epithelial Ovarian Cancer

Investigator's Agreement

I have read the attached protocol entitled "Atezolizumab in Combination with Neoadjuvant Chemotherapy and Interval Cytoreductive Surgery for Patients with Newly-Diagnosed Advanced-Stage Epithelial Ovarian Cancer", and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in **21 CFR Parts 11, 50, and 56.**

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Appendix 13 Dose Modifications and Day 1 Dosing Criteria

General Modifications

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic parameters have been met. Appendix 13 offers guidelines regarding dose modifications for chemotherapy that may be used at the discretion of the treating investigator.

1. Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC)

2. Lower limits for ANC and Platelet Count- Day 1 Dosing

    a. Day 1 of a subsequent cycle of cytotoxic chemotherapy will not be administered until the ANC is ≥ 1,000 cells/mcl and the platelet count is ≥ 75,000/mcl. All treatment will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive cytotoxic therapy.

       The day 8 and 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is at least 50,000/mcl. If not given, these doses are omitted and not made up

3. Use of hematopoietic Cytokines and Protective Agents

    a. It is anticipated that myelosuppression may be a significant side effect of the regimen. Myeloid growth factors (either filgrastim or pegfilgrastim) can be used (it is recommended that NCCN and/or ASCO guidelines be consulted). If myeloid growth factors are used, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after the last dose of chemotherapy and continuing through hematopoietic recover or pegfilgrastim will be administered at 6 mg subcutaneously (one dose per treatment cycle) 24-72 hours after the last dose of chemotherapy. Administration of growth factors on the same day as chemotherapy is not recommended. Pegfilgrastim is not recommended for chemotherapy regimens given less than every two weeks

    b. Patients will NOT receive prophylactic thrombopoietic agents.

c. Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They are not indicated in patients being treated with curative intent. They do not alleviate fatigue or increase energy. They should NOT be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.
http://www.fda.gov/Medwatch/safety/2007/safety07.htm

d. Patients may NOT receive amifostine or other protective agents.

Modifications for Hematologic Toxicity (Nadirs)

1. Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia, prolonged Grade 4 neutropenia persisting ≥ 7 days, delay of treatment for more than 7 days because of neutropenia, ANC <1000 cells/mcl on Day 1, or omission of day 8 or day 15 paclitaxel because of neutropenia. Febrile neutropenia is defined within CTCAE as a disorder characterized by an ANC <1000/mcl and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour

2. Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mcl) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/mcl), delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia, platelet count of <75,000/mcl on day 1, or inability to give day 8 or day 15 paclitaxel due to thrombocytopenia. There will be no modifications for uncomplicated Grade 3 thrombocytopenia except as above.

3. Initial occurrence of dose-limiting neutropenia or dose limiting thrombocytopenia will be handled according to the following table

Modification instructions for Dose-Limiting Hematologic Toxicity				
DLT ANC	**DLT PLT**	**First Occurrence**	**Second Occurrence**	**Third Occurrence**
Yes	No	Reduce carboplatin one AUC unit	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel	Reduce carboplatin one AUC, and give G-CSF after day 8 paclitaxel Fourth occurrence: Discontinue protocol directed cytotoxic therapy
Yes	Yes	Reduce carboplatin one AUC unit	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel) and reduce carboplatin one AUC unit	Discontinue protocol-directed cytotoxic therapy
No	Yes	Reduce carboplatin one AUC unit	Decrease carboplatin one AUC unit	Discontinue protocol-directed cytotoxic therapy

If treatment is delayed more than 21 days for reasons of toxicity, then protocol-directed cytotoxic therapy is ended; however patient may, at discretion of treating physician, continue with protocol directed maintenance therapy if she is benefiting from treatment.

In the event the patient has a third dose limiting hematologic toxicity but is still obtaining clinical benefit from chemotherapy, she may be treated with additional cycles of chemotherapy at the discretion of the investigator and with approval by Dr. Alvarez Secord. The need for additional dose modification will be determined on an individual basis.