A Phase II Trial of Atezolizumab plus Chemotherapy after Progression on PD-1 or PD-L1 Inhibitor in Cisplatin-ineligible Patients with Advanced Urothelial Carcinoma
HCRN GU17-295

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VERSION DATE:04FEB2022

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____
Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

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SYNOPSIS

TITLE	A Phase II Trial of Atezolizumab plus Chemotherapy after Progression on PD-1 or PD-L1 Inhibitor in Cisplatin-ineligible Patients with Advanced Urothelial Carcinoma
SHORT TITLE	Chemotherapy plus atezolizumab in patients with advanced cisplatin-ineligible urothelial carcinoma
PHASE	Phase 2, single arm
CONCEPT AND RATIONALE	The PD-L1 inhibitor, Atezolizumab, is FDA approved for first-line treatment in patients with metastatic urothelial carcinoma who are cisplatin ineligible. Patients who progress after first-line immune checkpoint inhibitors (Programmed cell death 1 [PD-1] or Programmed death-ligand 1 [PD-L1] inhibitors) have limited further treatment options. The concept of maintenance therapy with targeted agents and adding onto it at the time of disease progression is a proven effective strategy in several disease settings. Preclinical data indicates that cytotoxic chemotherapy can have an immunomodulatory effect and can potentially augment immune response. Based on these data, we hypothesize that in patients with cisplatin-ineligible urothelial carcinoma the use of atezolizumab in combination with chemotherapy after progression on PD-1 or PD-L1 inhibitor will result in clinical benefit.
OBJECTIVES	**Primary Objective** Evaluate PFS among patients to be treated with atezolizumab in combination with carboplatin + gemcitabine or docetaxel, who have cisplatin-ineligible metastatic urothelial carcinoma and who have progressed on prior PD-1 or PD-L1 inhibitor. **Secondary Objectives** • Assess the safety and tolerability of the combination of atezolizumab plus chemotherapy (carboplatin + gemcitabine or docetaxel) • Evaluate objective response rate (ORR) and clinical benefit rate (CBR), with RECIST 1.1 and irRECIST • Evaluate PFS with irRECIST • Evaluate overall survival (OS) • Compare PFS to historical controls. • Evaluate PFS among the subgroup treated with atezolizumab + carboplatin and gemcitabine • Evaluate PFS among the subgroup treated with atezolizumab + docetaxel

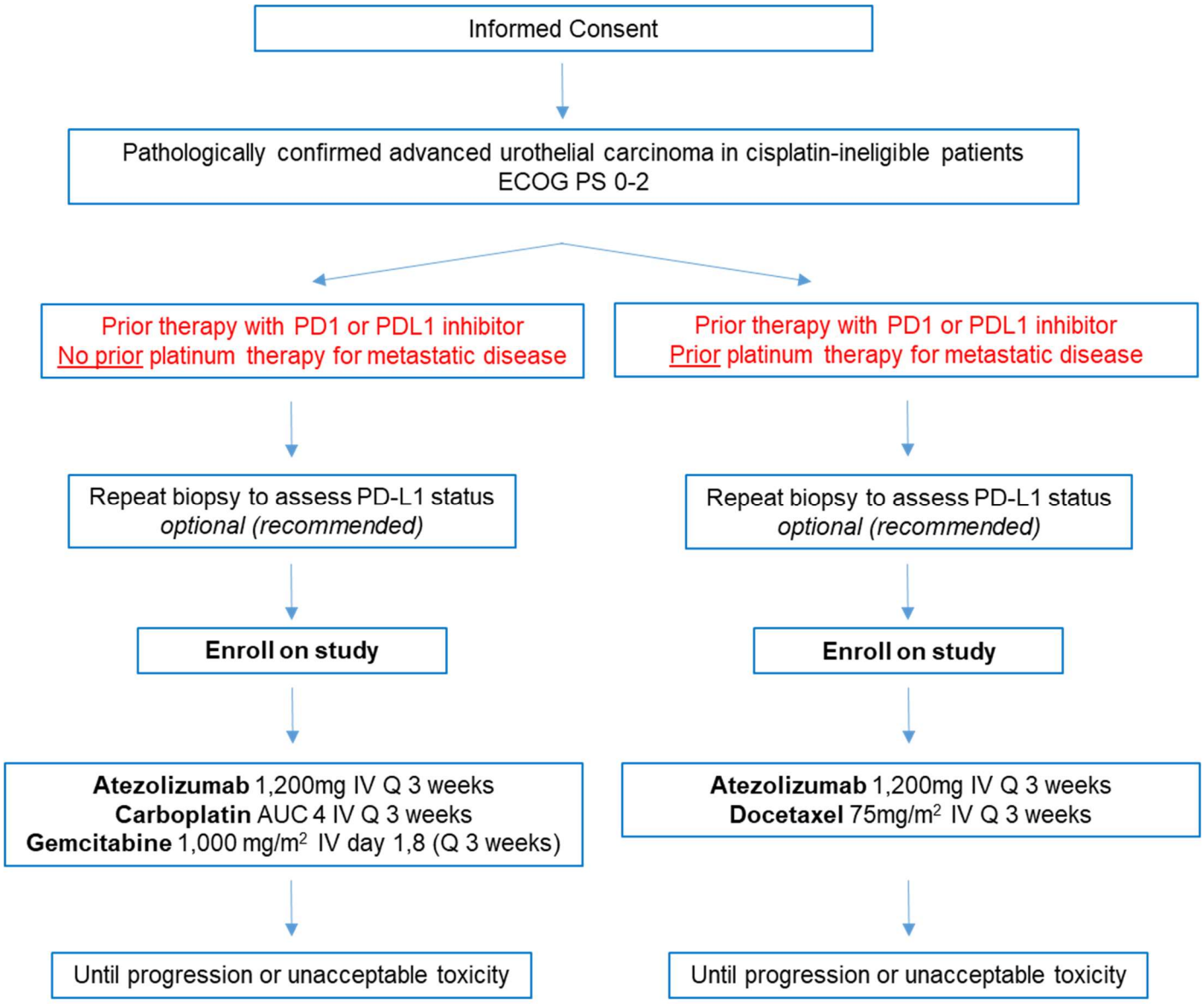
	Exploratory Objectives • Compare the efficacy of atezolizumab post disease progression with carboplatin + gemcitabine or docetaxel vs. treating with carboplatin + gemcitabine alone in a virtual control arm • Assess PD-L1 status at the following time-points: o REQUIRED, if available: Baseline from archival tissue (prior to treatment with PD-1 or PD-L1 inhibitor) o OPTIONAL (RECOMMENDED): From new biopsy prior to C1D1
KEY ELIGIBILITY CRITERIA **See Section 3 for a full set of eligibility criteria**	**Inclusion Criteria** 1. ECOG Performance status (PS) of 0-2 2. Histologically or cytologically confirmed metastatic or unresectable locally advanced urothelial carcinoma (primary tumor: renal pelvis, ureters, urinary bladder, or urethra) 3. Patients with mixed histologies are eligible 4. Cisplatin ineligible at the time of diagnosis with metastatic urothelial carcinoma based on consensus definition with any of the following criteria: ECOG PS 2, creatinine clearance <60mL/min, CTCAE v4 grade≥2 hearing loss, CTCAE v4 grade≥2 peripheral neuropathy, New York Heart Association (NYHA) class≥3 heart failure 5. Must have had progressive metastatic disease after previous treatment with PD-1 or PD-L1 inhibitor (in the adjuvant or metastatic setting). Treatment regimen will be determined based on prior treatment: o PD1 or PDL1 inhibitor with no prior platinum chemotherapy for metastatic disease → patients should be treated with atezolizumab + carboplatin + gemcitabine o Sequential or concurrent PD1/PDL1 inhibitor and carboplatin-based regimen → patients should be treated with atezolizumab + docetaxel 6. Most recent therapy does not have to have been a checkpoint inhibitor. Intercurrent treatment is acceptable as long as subjects meet all other inclusion criteria. 7. Previous neoadjuvant or adjuvant chemotherapy completed ≥ 6 months prior to enrollment is allowed **Exclusion Criteria** 8. Previous autoimmune complication from PD-1 or PD-L1 inhibitor requiring permanent discontinuation of therapy

INTERVENTION	Atezolizumab 1,200 mg IV Day 1, Carboplatin AUC 4 IV Day 1 and Gemcitabine 1,000 mg/m^2 IV Days 1 and 8 **OR** Atezolizumab 1,200mg IV Day 1 and Docetaxel 75mg/m^2 IV Day 1. Patients will be treated with Q21 day cycles until progressive disease or intolerable toxicity. Chemotherapy may be discontinued after 4-6 cycles per site investigator and/or patient's choice.
STATISTICAL METHODS	**Definition of primary endpoint** PFS is defined as the time from date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause; in the absence of an event, PFS will be censored at date of last disease assessment. **Definition of secondary endpoints** • ORR refers to the proportion of subjects with reduction in tumor burden of CR or PR according to RECIST 1.1 and immune-related response criteria (irRECIST) criteria • CBR is defined by stable disease (SD) for at least 3 months, PR, or CR by both RECIST 1.1 and irRECIST criteria • OS defined by the date of treatment start to date of death from any cause • PFS is defined as the time from date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause; in the absence of an event, PFS will be censored at date of last disease assessment. **Analytic Plan** The PFS along with 95% CI will be estimated using the Kaplan-Meier method using the Efficacy population. • ORR and clinical benefit rate will be estimated with two-sided 95% exact binomial confidence intervals. • Toxicities will be tabulated. Change in tumor levels of PD-L1 will be descriptively summarized and compared over time using paired t-tests. Proportional hazards regression (for PFS) and logistic regression (for ORR and clinical benefit rate) will be used to explore the association between biomarkers with clinical outcomes.
TOTAL NUMBER OF SUBJECTS	N=37 to achieve 30 events (an event is defined as a patient with progression or death). We hypothesize that patients receiving atezolizumab plus chemotherapy (carboplatin + gemcitabine or docetaxel) will have a median PFS of 0.6 year (7.2 months).

	Under the exponential distribution assumption, this corresponds to an annual hazard rate of 1.155. The number of events is 30 required to obtain a 95% confidence interval of [0.79, 1.60] for estimating the hazard rate. Of note, the historical data suggest a median PFS of 4 months, which corresponds to a hazard rate of 2.08, well outside the anticipated 95% CI. A sample size of 33 is expected to yield 30 events, assuming an accrual period of 24 months (1.375 per month) and maximum follow-up of 18 months after the last patient is enrolled. To allow for replacement of patients who are not evaluable for efficacy (estimated to be 10%), up to 37 patients will be enrolled.
ESTIMATED ENROLLMENT PERIOD	Estimated 24 months
ESTIMATED STUDY DURATION	Estimated 42 months

TABLE OF CONTENTS

SCHEMA


Informed Consent
Pathologically confirmed advanced urothelial carcinoma in cisplatin-ineligible patients
ECOG PS 0-2
Prior therapy with PD1 or PDL1 inhibitor
No prior platinum therapy for metastatic disease
Prior therapy with PD1 or PDL1 inhibitor
Prior platinum therapy for metastatic disease
Repeat biopsy to assess PD-L1 status
optional (recommended)
Repeat biopsy to assess PD-L1 status
optional (recommended)
Enroll on study
Enroll on study
Atezolizumab 1,200mg IV Q 3 weeks
Carboplatin AUC 4 IV Q 3 weeks
Gemcitabine 1,000 mg/m2 IV day 1,8 (Q 3 weeks)
Atezolizumab 1,200mg IV Q 3 weeks
Docetaxel 75mg/m2 IV Q 3 weeks
Until progression or unacceptable toxicity
Until progression or unacceptable toxicity

1. BACKGROUND AND RATIONALE

1.1 Background of urothelial carcinoma

Urothelial bladder cancer is the most common cancer of the urinary system worldwide, with transitional cell carcinoma (TCC) of the bladder being the predominant histologic type and location. Urothelial cancers may less commonly originate in the renal pelvis, ureters, or urethra. Urothelial carcinoma is the ninth most common cancer worldwide and more than 165,000 patients die from this disease annually.[1]

1.2 Current Standard of Care in the treatment of advanced urothelial carcinoma

The current standard of care for treatment of patients with metastatic urothelial carcinoma is cisplatin-based combination chemotherapy. Nonetheless, a significant number of patients are not appropriate candidates for cisplatin-based combination chemotherapy because of comorbidities and impaired functional status.[2] A consensus-working group has defined medically frail patients as those with the following criteria predisposing them to increased risks of toxicity with cisplatin-based chemotherapy[3]:

- World Health Organization (WHO)/ECOG performance status ≥ 2 or a KPS of 60% to 70%
- Creatinine clearance < 60 mL/min
- A hearing loss of 25 dB at two contiguous frequencies
- Grade ≥ 2 peripheral neuropathy
- New York Heart Association Class ≥ III heart failure

For cisplatin-ineligible patients, treatment options include carboplatin-based, non−platinum-based, single-agent chemotherapy regimens, or even best supportive care (BSC).

1.2.1 Cisplatin-based Regimens

Patients with previously untreated urothelial bladder cancer typically receive platinum-based chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced urothelial carcinoma came in the mid-1980s; two studies showed that the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) produced overall response rates greater than 70%, with approximately 35% of patients achieving a complete response (CR).[4,5] Subsequently, two prospective, randomized, Phase III trials demonstrated the superiority of MVAC in patients with advanced disease. MVAC was tested against single-agent cisplatin in a multicenter U.S. Intergroup trial.[6] Compared with cisplatin, MVAC demonstrated significant improvements in the overall response rate (39% vs. 12%) and median overall survival (OS; 13 vs. 8 months). MVAC was also compared with the combination of cisplatin, cyclophosphamide, and doxorubicin (CISCA) in patients with advanced UBC.[7] The objective response rate (ORR) of MVAC was 65% versus 46% for the CISCA arm and demonstrated a superior median OS (62.6 vs. 40.4 weeks). In an effort to develop a less toxic regimen, the combination of gemcitabine and cisplatin was tested against MVAC in the Phase III setting following the demonstration of activity in earlier phase trials. In the Phase III trial, 405 patients with advanced TCC of the urothelium were randomly assigned to GC versus MVAC for a maximum of six cycles. Patients allocated to gemcitabine and cisplatin had a similar OS to those randomized to MVAC (14.0 months for GC vs. 15.2 months for MVAC; hazard ratio [HR] = 1.09; 95% CI: 0.88, 1.34, p = 0.66) with less Grade 3 or 4 toxicity (including neutropenia,

neutropenic sepsis, and mucositis) and, as a result, GC has largely displaced MVAC as the standard of care.[8] The benefit conferred by cisplatin-based chemotherapy regimens appears to have reached a plateau in median OS (13−15 months) and leaves a significant population in need of salvage therapy options.

1.2.2 Carboplatin-based Regimens

Poor performance status, impaired renal function, advanced age, and multiple comorbidities (e.g., neuropathy, congestive heart failure, and hearing loss) are fairly common in patients with advanced urothelial carcinoma and can prohibit the use of cisplatin-based regimens. Carboplatin-based regimens are feasible in these patients, but trials suggest they are less effective than cisplatin-based regimen.[9] The benefit of carboplatin-based therapy in medically "unfit" patients was demonstrated in the European Organization for the Research and Treatment of Cancer (EORTC) Trial 30986. In this study, 238 patients with previously untreated advanced UBC and either a poor performance status and/or impaired renal function (glomerular filtration rate [GFR] < 60 but > 30 mL/min) were enrolled to gemcitabine and carboplatin (CarboGem) or methotrexate, carboplatin, and vincristine (M-CAVI).[10] The ORR of CarboGem was 41% versus 30% for the M-CAVI arm and demonstrated no difference in the median OS (9.3 vs. 8.1 months). Notably, those with both impaired renal function and poor performance status had especially poor outcomes and increased acute toxicity with combination chemotherapy in this trial.

1.2.3 Immunotherapy in urothelial carcinoma

Immunotherapy was first found to be effective in non-muscle invasive bladder cancer in 1976 with the introduction of BCG.[11] Recently immunotherapy, in particular the immune checkpoint inhibitor for programmed death ligand-1 (PD-L1), atezolizumab, has been found to be clinically active in patients with locally and advanced and metastatic urothelial carcinoma who progressed after treatment with platinum-based chemotherapy. PD-1 is a T-cell co-receptor that, when activated, suppresses antitumor immunity by its interaction with its ligands, PD-L1 and PD-L2.

In a single arm multicenter phase II trial, 310 patients with advanced urothelial carcinoma were treated with atezolizumab in the second line setting at a dose of 1200 mg, given every 3 weeks.[12] This study demonstrated durable activity and good tolerability in patients with urothelial carcinoma who had progressed after platinum-based first line therapy. The overall objective response rate was 15% (95% CI, 11 to 19). Moreover, increased expression of PD-L1 on immune cells was associated with increased response: patients with high PD-L1 expression had higher response rates 26% (95% CI, 18 to 36) compared to patients with lower PD-L1 expression 18% (95% CI, 13 to 24). Based on this study, the food and drug administration (FDA) granted atezolizumab accelerated approval for second-line therapy of metastatic urothelial carcinoma in May 2016.

In a single arm multicenter phase II trial, 123 previously untreated patients with locally advanced or metastatic urothelial cancer who were cisplatin-ineligible were treated with atezolizumab 1200 mg every 21 days until disease progression.[13] At a median follow-up of 17.2 months, the objective response rate was 23% (95% CI, 16 to 31) and the complete response rate was 9% (11 complete responses). Atezolizumab achieved durable responses and was generally tolerated by

patients. Based on these results, atezolizumab was granted accelerated FDA approval in first-line treatment of patients with urothelial carcinoma who are cisplatin-ineligible in April 2017.

In addition to studies with atezolizumab, 2 recently reported phase 2 trials and 1 phase 3 trial have shown efficacy of programmed death receptor 1 (PD-1) inhibitors in metastatic urothelial carcinoma. CheckMate 275 was a single arm phase II study of Nivolumab in patients with urothelial carcinoma that progressed after platinum-based chemotherapy.[14] At a median follow-up of 7 months, overall response rate was 19.6% (95% CI 15 to 24.9). KEYNOTE-052 was a single arm phase II study of pembrolizumab as first line in patients with cisplatin-ineligible urothelial carcinoma.[15] With a median follow-up of 8 months, overall response rate was 24% (95% CI, 16-33.6). Patients with higher PD-L1 expression had more response rates. KEYNOTE-045 was a phase III study of pembrolizumab vs. investigator's choice chemotherapy in 2nd line metastatic urothelial carcinoma.[16] Median overall survival was 10.3 months in the pembrolizumab group compared to 7.4 months in the in the chemotherapy group.

In patients with cisplatin-ineligible urothelial carcinoma who progress after first-line PD-1 or PD-L1 inhibitor, cytotoxic chemotherapy will have modest response rates and improvement in survival. Several phase II trials have evaluated a variety of non-cisplatin based chemotherapy regimens for patients with urothelial carcinoma who are not eligible for cisplatin. These regimens included carboplatin/gemcitabine, single agent gemcitabine, carboplatin/paclitaxel, and gemcitabine/paclitaxel. Average response rates ranged between 20-40% and median progression-free survival (PFS) ranged between 3-5 months.[10,17-21]

1.3 Background of 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.[12,22] 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.

Please refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.4 Background and rationale of combination chemotherapy and atezolizumab in patients with advanced urothelial carcinoma

Currently, metastatic urothelial carcinoma in cisplatin-ineligible patients is optimally treated with single agent checkpoint inhibition (atezolizumab and pembrolizumab are FDA approved in this setting) or combination chemotherapy with carboplatin + gemcitabine. This regimen has well known 'macro' effects on the immune system such as neutropenia and lymphopenia; however, the effects on tumor-specific immune responses are becoming better appreciated. The ability to augment immune effector and suppressor cells and cytokine milieu can be taken advantage of to beneficially modulate atezolizumab immune checkpoint therapy.[23-26]

Active Bladder Cancer Agent	Immune Effects
Cisplatin or Carboplatin	Class I HLA expression Inhibits STAT6 expression of PD-L2 (B7-DC) Enhance Fas/ICAM-1 expression for Ag specific CTL killing
Gemcitabine	Increased Ag presentation Inhibit and reduce myeloid derived suppressor cells Enhance Fas expression CD40 based T cell stimulation Prevent PD-1 dependent CD4+ T-cell tolerization
Immune modulating effects of cytotoxic chemotherapy for bladder cancer. ENREF_43 DC, dendritic cell; HLA, human leukocyte antigen; Ag, antigen; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex	

Cisplatin or carboplatin can stimulate antigen presentation, increase HLA expression, and improve factors for cytotoxic T lymphocyte kill. It also inhibits STAT6 expression of PD-L2 which has unknown effects on PD-1 inhibition and tumor surveillance, though likely does not impede it.[24,25]

Gemcitabine has been shown in vivo and in clinical trials to favorably augment tumor specific CD4+ and CD8+ ratios and to induce responses through effects it also has on the B-lymphocytes.[27,28] Gemcitabine, reduces myeloid-derived suppressor cells (MDSCs) to enhance immune surveillance[23] and also prevents PD-1 dependent CD4+ T cell tolerization.[26]

Several ongoing clinical trials combining immune checkpoint inhibitors with platinum-based chemotherapy in non-small cell lung cancer have demonstrated manageable toxicities.[29-31] In an interim report of the Phase I multi-arm trial of an anti-PD-1 inhibitor in combination with 3 different platinum doublet regimens for NSCLC, the cisplatin + gemcitabine combination arm showed good tolerability without any treatment discontinuations and grade 3-4 toxicity limited to anemia, thrombocytopenia, and 1 event of pneumonitis.[29] Ongoing studies in metastatic colon cancer demonstrated safety of combining immune checkpoint inhibitor therapy with 5-fu, oxaliplatin, and leucovorin.[32]

In metastatic urothelial carcinoma, the combination of checkpoint inhibition with cytotoxic chemotherapy has been shown to be feasible.[33] A phase 3 study is underway comparing atezolizumab as monotherapy or in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma (NCT02807636). A phase IB

trial is evaluating the combination of atezolizumab with bevacizumab and/or cytotoxic chemotherapy in patients with advanced solid tumors (NCT01633970).

Treatment with carboplatin and gemcitabine is a standard of care option for cisplatin-ineligible patients with metastatic urothelial carcinoma. Myelosuppression/cytopenias is a dose limiting toxicity of gemcitabine; and myelosuppression/nausea are the most common and/or serious adverse events for carboplatin. The most common adverse events identified (~10%) to date for atezolizumab are fatigue, nausea, and less commonly, flu-like symptoms and are often grade 1-2. Hematologic toxicity has not been noted. As atezolizumab toxicities are infrequent and mild, there is very little expectation for overlapping toxicities.

1.5 Rationale of combination Chemotherapy and Atezolizumab after progression on PD1 or PDL1 inhibitor

The concept of maintenance therapy with targeted agents and adding onto it at the time of disease progression is a proven effective strategy in several disease settings. For example, in patients with metastatic colon cancer the continued use of Bevacizumab (combined with a new chemotherapy agent) beyond progression has resulted in improved survival when compared with abandoning Bevacizumab and changing to a new chemotherapy agent alone.[34] Similarly, the continued use of Trastuzumab in combination with chemotherapy after progression on Trastuzumab in HER2neu positive metastatic breast cancer improves outcomes in patients with breast cancer compared with abandoning HER-2 therapy and switching to chemotherapy alone.[35]

The combination of immunotherapy with checkpoint inhibitors and cytotoxic chemotherapy has been shown to be safe and feasible in early studies with urothelial carcinoma.[36]

The mechanism of resistance to PD-1 and PD-L1 inhibitors after prior response is poorly understood. As seen in prior trials evaluating PD-1 and PD-L1 inhibitors in urothelial carcinoma, there are patients whose tumors express PD-L1 that do not respond, and patients without PD-L1 expression who have sustained response to PD-1 or PD-L1 inhibitors. Although data are lacking in this area, there are many theories about both the intrinsic and acquired resistance to immune checkpoint inhibitors.

It has been shown in many tumor types that the presence of lymphocytic infiltrates with CD4 and CD8 T-cells within the tumor correlates with better outcomes. The principle of immune checkpoint inhibitors is to reactivate the endogenous tumor-specific T-cell immune response leading to tumoricidal activity. However, there is a subset of patients whose tumors lack lymphocytic infiltrates or who fail to produce a T-cell response with immune therapy thereby having intrinsic resistance. Tumors with low mutational burden have also been shown to have intrinsic resistance to the immune checkpoint inhibitors, likely by expressing fewer antigens that are recognized as foreign by the immune system, hence more likely to evade immune detection compared to tumors with a higher mutational load such as smoking-related urothelial carcinoma. The last theory is that the tumor microenvironment may prevent T-cells from exerting their effector function leading to intrinsic resistance. TGF-b, IL-10 and IDO are inhibitory molecules that have a direct negative effect on T-cell function in the microenvironment. The immature dendritic cells, myeloid derived suppressor cells or (inducible) regulatory CD4 T-cells within the microenvironment may also have an indirect effect on immune therapy. Additionally, the loss of

MHC class 1 expression in certain tumor cell population/subclones or other defects in antigen processing cascade may cloak the tumor cells from the immune system.

Therapy-induced resistance, occurs when patients initially respond to immunotherapy then relapse or progress. This may be a result of immune-editing. This occurs when a heterogeneous tumor selects out clones that lack antigens that stimulate the immune response resulting in immune evasion. To overcome resistance, it is possible that pre-conditioning of the tumor in the form of chemotherapy, or radiation therapy may promote an immune supportive tumor microenvironment that may re-sensitize the tumors to the effects of immune therapy.[37]

Based on these data, we hypothesize that in patients with cisplatin-ineligible urothelial carcinoma, the continued use of immune checkpoint inhibition with atezolizumab in combination with chemotherapy after progression on PD-1 or PD-L1 inhibitor will result in clinical benefit.

The combination of carboplatin and gemcitabine was the standard first-line therapy for patients with cisplatin-ineligible metastatic urothelial carcinoma until the FDA approval of atezolizumab and pembrolizumab in the first-line setting. For patients treated with first-line atezolizumab or pembrolizumab, the combination of carboplatin and gemcitabine has now become second-line therapy. Docetaxel remains a treatment option in patients who progress after platinum-based chemotherapy and immune checkpoint inhibitors.[47]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Evaluate PFS among patients to be treated with atezolizumab in combination with carboplatin + gemcitabine or docetaxel, who have cisplatin-ineligible metastatic urothelial carcinoma and who have progressed on prior PD-1 or PD-L1 inhibitor.

2.1.2 Secondary Objectives

- Assess the safety and tolerability of the combination of atezolizumab plus chemotherapy (carboplatin + gemcitabine or docetaxel)
- Evaluate objective response rate (ORR) with RECIST 1.1 and irRECIST
- Evaluate clinical benefit rate (CBR) with RECIST 1.1 and irRECIST
- Evaluate PFS with irRECIST
- Evaluate overall survival (OS)
- Compare PFS compared to historical controls.
- Evaluate PFS for atezolizumab + carboplatin and gemcitabine
- Evaluate PFS for atezolizumab + docetaxel

2.1.3 Correlative/Exploratory Objectives

- Compare the efficacy of atezolizumab post disease progression with carboplatin + gemcitabine or docetaxel vs. treating with carboplatin + gemcitabine alone in a virtual control arm
- Assess the PD-L1 status of the tumor at the following time points:
    - REQUIRED, if available: Baseline from archival tissue (prior to treatment with PD-1 or PD-L1 inhibitor)
    - OPTIONAL (RECOMMENDED): From new biopsy (prior to C1D1)

2.2 Endpoints

2.2.1 Primary Endpoint

PFS is defined as the time from date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause; in the absence of an event, PFS will be censored at date of last disease assessment.

2.2.2 Secondary Endpoints (See Section 9 for definitions)

- Toxicity will be assessed using CTCAE v4.03
- Objective response rate (ORR) using RECIST 1.1 defined as the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).
- ORR defined as the proportion of all subjects with confirmed PR or CR using immune-related response criteria (irRECIST), from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).
- Clinical benefit rate (CBR) of treatment (defined by proportion of all subjects with stable disease for at least 3 months, partial response, or complete response) using RECIST 1.1 from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).
- CBR of treatment (defined by proportion of all subjects with stable disease for at least 3 months, partial response, or complete response) using irRECIST from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).
- PFS defined as duration from date of treatment start until progression according to irRECIST criteria or death from any cause
- OS defined by the date of treatment start to date of death from any cause

2.2.3 Exploratory Endpoints

- Efficacy of atezolizumab+carboplatin+gemcitabine in this trial compared to carboplatin+gemcitabine in the virtual control arm will be compared using OS defined by the date of treatment start to date of death from any cause.
- Assess PD-L1 status of tissue samples (archived tissue and new biopsy after progression on PD-1 or PD-L1 inhibitor) using PD-L1 immunohistochemistry assay.

2.2.4 Virtual Control Arm

Flatiron Electronic Health Records will serve as data source for a retrospective real-world analysis of patient level data. The data source will be queried for patients with metastatic urothelial carcinoma who received first-line treatment with atezolizumab and then had progressive disease treated with carboplatin+gemcitabine. This data source will be queried for OS analysis and hence serve as a virtual control arm to the single arm phase II trial in this protocol. Data exports will be performed at 2 time-points by HCRN staff. OS analysis of data exports in the virtual control arm will be the responsibility of the sponsor investigator and the Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Cancer Center (IUSCC).

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. ECOG Performance Status of 0-2 within 28 days prior to registration.

4. Histological or cytological confirmed metastatic or unresectable locally advanced urothelial carcinoma (primary tumor: renal pelvis, ureters, urinary bladder, or urethra).

5. Patients with mixed histologies are eligible.

6. Cisplatin ineligible at the time of diagnosis with metastatic urothelial carcinoma based on consensus definition with any of the following criteria: ECOG PS 2, creatinine clearance < 60mL/min, CTCAE v4 grade ≥ 2 hearing loss, CTCAE v4 grade ≥ 2 peripheral neuropathy, New York Heart Association (NYHA) class ≥ 3 heart failure.

7. Measurable disease according to RECIST 1.1 within 28 days prior to registration.

8. Must have had progressive metastatic disease after previous treatment with PD-1 or PD-L1 inhibitor (in the adjuvant or metastatic setting). Treatment regimen will be determined based on prior treatment:
    - PD1 or PDL1 inhibitor with no prior platinum chemotherapy for metastatic disease → patients should be treated with atezolizumab + carboplatin + gemcitabine on trial.
    - Sequential or concurrent PD1/PDL1 inhibitor and carboplatin-based regimen → patients should be treated with atezolizumab + docetaxel on trial.

9. Most recent therapy does not have to have been a checkpoint inhibitor. Intercurrent treatment is acceptable if subjects meet all other inclusion criteria.

10. A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis at least 4 weeks prior to study registration, have been off of corticosteroids for ≥ 2 weeks, and are asymptomatic.

11. Previous neoadjuvant or adjuvant chemotherapy that was completed ≥ 6 months prior to study enrollment is allowed.

12. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
White blood cell (WBC)	≥ 2 k/mm^3
Absolute Neutrophil Count (ANC)	≥ 1.5 K/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Platelet	>100k
Renal	
Estimated creatinine clearance[1]	≥ 30 mL/min
Hepatic	
Bilirubin	1.5 ≤ (ULN)[2]
Aspartate aminotransferase (AST)	≤ 1.5 × ULN
Alanine aminotransferase (ALT)	≤ 1.5 × ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 2 × ULN (**NOTE:** This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose)

[1] Cockcroft-Gault formula will be used to calculate creatinine clearance
[2] Except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL

13. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test within 28 days prior to registration. These women must also have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of atezolizumab then every 6 weeks thereafter. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is post-menopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

14. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 150 days (5 months) after treatment discontinuation. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

15. Men who are sexually active with FOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving atezolizumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 150 days (5 months) after the last dose of investigational product.

16. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Previous autoimmune complication from PD-1 or PD-L1 inhibitor requiring permanent discontinuation of therapy.

2. Previous permanent discontinuation from PD-1 or PD-L1 inhibitor due to an adverse event (patients who had temporary holds or discontinuation of PD-1 or PD-L1 inhibitor and then re-treated are eligible).

3. Any serious or uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy.

4. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

5. Has a known additional malignancy that is progressing or required treatment ≤ 48 months of study registration. Exceptions: include malignancies with negligible risk of metastasis or death treated with expected curative outcome or undergoing surveillance per investigator's discretion (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, ductal carcinoma in situ treated surgically with curative intent, or very low risk or low risk prostate cancer per NCCN guidelines).

6. Active central nervous system (CNS) metastases. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression within 28 days prior to the first dose of atezolizumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

7. Treatment with any investigational drug within 30 days prior to registration.

8. Subjects with an active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger. (Subjects with vitiligo, autoimmune thyroiditis, or type I diabetes mellitus are permitted to enroll.).

9. As there is potential for hepatic toxicity with atezolizumab, drugs with a predisposition to hepatoxicity should be used with caution in subjects treated with atezolizumab-containing regimen.

10. Subjects should be excluded if they have known history of testing positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. Testing is not required.

11. Subjects should be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing is not required.

12. History of allergy to atezolizumab or respective chemotherapy regimen (carboplatin + gemcitabine or docetaxel).

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy **within 5 business days** of registration.

5. TREATMENT PLAN

This is a single arm phase II study assessing the activity of atezolizumab in combination with carboplatin + gemcitabine or docetaxel compared to historical controls of chemotherapy only in metastatic or recurrent urothelial carcinoma subjects. Subjects that received a PD 1 or PD-L1 inhibitor with no prior platinum chemotherapy for metastatic disease will be treated with atezolizumab + carboplatin + gemcitabine on trial. Subjects that received sequential or concurrent PD1/PDL1 inhibitor and carboplatin-based regimen will be treated with atezolizumab + docetaxel on trial.

5.1 Pre-medications and Hydration

There are no required pre-medications or intravenous hydration for treatment with carboplatin, gemcitabine, docetaxel, or atezolizumab. Institutional standards will be followed for pre-medications and/or intravenous hydration for treatment with either carboplatin, gemcitabine, docetaxel, or atezolizumab.

5.2 Treatment Administration

5.2.1 Carboplatin, Gemcitabine, and Atezolizumab Administration

Drug[1]	Dose[2]	Route	Schedule	Cycle Length
Carboplatin	AUC 4	Intravenously (IV) per institutional standards	Day 1	3 weeks (21 days)
Gemcitabine	1,000 mg/m^2	IV per institutional standards	Day 1 and 8	
Atezolizumab	1,200 mg	IV over 1 hour	Day 1	

[1] Carboplatin will be infused first followed by gemcitabine then atezolizumab. Atezolizumab will be administered a minimum of 5 minutes *after* carboplatin and gemcitabine
[2] Medication dose will not be changed for reasons other than weight change per institutional policy

NOTE: * Infusions may be given ± 3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in patient's chart and case report forms.

5.2.2 Docetaxel and Atezolizumab Administration

Drug[1]	Dose[2]	Route	Schedule	Cycle Length
Docetaxel	75mg/m^2	IV per institutional standards	Day 1	3 weeks (21 days)
Atezolizumab[3]	1,200 mg	IV over 1 hour	Day 1	

[1] Docetaxel will be infused first followed by atezolizumab. Atezolizumab will be administered a minimum of 5 minutes *after* docetaxel.
[2] Medication dose will not be changed for reasons other than weight change per institutional policy.

5.2.3 Carboplatin Administration

Carboplatin AUC 4 will be administered intravenously per institutional standards on Day 1 of each 21 day Cycle. Please see package insert for additional details regarding this medication.

5.2.4 Gemcitabine Administration

Gemcitabine 1,000mg/m^2 will be administered intravenously per institutional standards on Days 1 and 8 of each 21 day Cycle. Please see package insert for additional details regarding this medication.

5.2.5 Docetaxel Administration

Docetaxel 75 mg/m^2 will be administered intravenously per institutional standards on Day 1 of each 21 day Cycle. Please see package insert for additional details regarding this medication.

5.2.6 Atezolizumab Administration

Atezolizumab will be delivered over 60 minutes (± 15) intravenously on Day 1 of each 21 day Cycle. Institutional standards will be used regarding the infusion. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Guidelines for management of atezolizumab-specific adverse events can be found in Appendix 1. Please see the investigator's brochure for additional details regarding this medication.

5.3 Study Treatment Adjustments

Chemotherapy (carboplatin + gemcitabine or docetaxel) may be discontinued after 4-6 cycles per site investigator and/or patient's choice.

Atezolizumab should be continued until disease progression per RECIST v1.1 or loss of clinical benefit, unacceptable toxicity, or consent withdrawal. **NOTE:**

- Patients with progression by RECIST 1.1 may continue treatment with atezolizumab if they demonstrate clinical benefit per investigator's assessment.
- Patients who have achieved a PR or CR of target lesions and who develop new lesions that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next assessment and continue to demonstrate clinical benefit per investigator.

5.4 Concomitant Medications

All concomitant medications should be reported to the site investigator and recorded on the appropriate eCRF.

5.4.1 Allowed Concomitant Medications

Patients are permitted to use the following therapies during the study:

- Growth factor support may be delivered at the site investigator's discretion
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:
    - Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). If clinical benefit is observed, treatment with atezolizumab may be continued during palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of

treatment, anatomical site, dose administered and fractionation schedule, and adverse events.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:
    - Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the site investigator. In general, site investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local 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 β2-adrenergic agonists. Retreating with medication will be at discretion of investigator.

5.4.2 Prohibited Concomitant Medications

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) whether health authority-approved or experimental, is prohibited until disease progression is documented and the patient has discontinued study treatment (with the exception of palliative radiotherapy and local therapy under certain circumstances – see Section 5.3.1 for details).
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 30 days prior to initiation of study treatment and during study treatment.
- Denosumab (a RANKL inhibitor) is prohibited during the atezolizumab treatment because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead during atezolizumab treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL 2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

6 Toxicities and Dose Delays/Dose Modifications

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays for Atezolizumab

Management of atezolizumab-specific adverse events can be found in Appendix 1. Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to atezolizumab). All study drugs must be delayed until treatment can resume.

Atezolizumab administration should be delayed for the following:

Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Grade 3 skin, drug-related AE

Grade 3 drug-related laboratory abnormality, with the following exceptions:

- Grade ≤ 3 lymphopenia or leukopenia does not require dose delay.
- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has a baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The sponsor-investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

Any AE, laboratory abnormality, or inter-current illness which, in the judgment of the site investigator, warrants delaying the dose of study medication.

Subjects who require delay of atezolizumab should be re-evaluated weekly or more frequently if clinically indicated and resume atezolizumab dosing when re-treatment criteria are met.

Patients may temporarily suspend study treatment for up to 42 days beyond the last dose if they experience adverse events that require a dose to be held. If atezolizumab is held because of adverse events for > 42 days beyond the last dose, then the patient will be discontinued from atezolizumab and will be followed for safety and efficacy.

If, in the judgment of the site investigator, the patient is likely to derive clinical benefit from atezolizumab after a hold of > 42 days, study drug may be restarted with the approval of the sponsor-investigator. If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be held for additional time beyond 42 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable

length of interruption will depend on an agreement between the site investigator and sponsor-investigator.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with sponsor-investigator approval. The acceptable length of interruption will depend on agreement between the site investigator and the sponsor-investigator.

6.1.1 Criteria to Resume Treatment with Atezolizumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST, ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST, ALT or total bilirubin may resume treatment in the presence of Grade 2 AST, ALT OR total bilirubin
- Subjects with combined Grade 2 AST, ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month will be eligible to restart treatment at the discretion of the treating physician.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment at the discretion of the treating physician.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time-point per protocol. However, if the treatment is delayed past the next scheduled time-point per protocol, the next scheduled time-point will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified abpve

6.1.2 Discontinuation Criteria for Atezolizumab

Patients must permanently discontinue study treatment (atezolizumab and/or carboplatin plus gemcitabine) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune mediated adverse event determined by the site investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Site investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the site investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Patients will discontinue treatment at occurrence of progression with the following exception: Patients who have achieved a PR or CR of target lesions and who develop new lesions that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next assessment and continue to demonstrate clinical benefit per investigator.

The primary reason for study treatment discontinuation should be documented in the patient's medical records.

Patients will return to the clinic for a treatment discontinuation visit around 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities.

Subjects will be followed up to 18 months after the last patient is enrolled onto the study. Information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits.

6.1.3 Dose Modifications for Atezolizumab Dose modifications on Day 1

Dose reductions or dose escalations of atezolizumab are not permitted. If treatment with carboplatin+gemcitabine or docetaxel is delayed, atezolizumab dosing should be delayed as well and should resume to stay "in-sequence" with carboplatin + gemcitabine or docetaxel cycles.

6.1.4 Management of Atezolizumab-Specific Adverse Events

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-mediated adverse events 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-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The primary approach to Grade 1−2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune-mediated adverse events, atezolizumab should be held and oral/parenteral steroids administered. Recurrent Grade 2 immune-mediated adverse events may also mandate withholding atezolizumab or the use of steroids. Consideration for benefit-risk balance should be made by the site 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 immune-mediated adverse events.

Management of systemic immune activation is presented below. See the Atezolizumab Investigator's Brochure for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events.

6.2 Dose Modifications for Carboplatin and Gemcitabine

6.2.1 Hematologic adjustments

Complete white blood cell (WBC) and platelet count weekly on days 1 and 8 in every cycle. Absolute neutrophils count (ANC) is recommended and is mandatory whenever WBC < 3.0 x 10^9/l. Grade 3 febrile neutropenia should be retreated after recovery.

Dose modifications on Day 1

WBC x 10^9/l		**ANC x 10^9/l**		**Platelets x 10^9/l**	**% dose of Gemcitabine**	**% dose of Carboplatin**
≥ 3.0	and	≥ 1.5	and	≥ 100	100	100
< 3.0	and	≥ 1.5	and	≥ 100	100	100
< 3.0	or	< 1.5	or	< 100	Delay 1 week	Delay 1 week

Dose modifications on Day 8

WBC x 10^9/l		**ANC x 10^9/l**		**Platelets x 10^9/l**	**% dose of Gemcitabine**
≥ 3.0	and	≥ 1.5	and	≥ 100	100
≥ 2.0 – 3.0	and	≥ 1.0	and	> 100	100
1.0 – 1.9	or	>0.5 - <1.0	or	50-99	50
< 1.0	or	<0.5	or	< 50	Withhold

NOTE: If treatment with carboplatin and gemcitabine is delayed per guidelines in 6.1.6.1, atezolizumab dosing should be delayed as well and should resume to stay "in-sequence" with carboplatin + gemcitabine cycles.

Dose modifications for subsequent cycles

At day 1, 25% dose reduction of carboplatin and gemcitabine if during the nadir one or more of the following occurs:

- grade IV neutropenia (ANC < 0.5 x 109/l) with fever > 38.5 C or
- grade IV thrombocytopenia (<10.0 x 109/l) for more than 3 days or
- thrombocytopenia with active bleeding during the nadir.

If a patient requires more than 2 weeks for hematologic recovery (defined as at least WBC is ≥ 2.0 x 10^9/l, ANC ≥ 1.0 x 10^9/l and platelets ≥ 75 x 10^9/l), treatment should be continued with 75% of both drugs.

6.2.2 Renal Toxicity

- Carboplatin will be adjusted every cycle using Calvert's formula.
- For gemcitabine, no dose modification is necessary if the GFR is ≥ 30 ml/min. Gemcitabine is withheld if the GFR is less than 30 ml/min.

6.2.3 Hypersensitivity reaction adjustments

- No dose reductions will be made for any hypersensitivity reactions. If a subject experiences a hypersensitivity reaction, treatment should be as indicated below:
    - Grade 1 symptoms (eg., mild flushing, rash, pruritis) = complete infusion. Supervise at bedside. No treatment required.
    - Grade 2 symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) = Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a slower rate, then increased incrementally to the initial planned rate. Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment and the rate of infusion should be decreased initially and then increased back to the recommended 1 hour infusion.
    - Grade 3 symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria) = Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The subject will go off study
    - Grade 4 symptoms = Anaphylaxis—Discontinue protocol treatment.

6.2.4 Other non-hematologic toxicities

- Grade ≥ 3 AE = carboplatin and gemcitabine should be held until resolution to Grade 1 or less, then reinstituted, if medically appropriate, after recovery.
- Subjects requiring a > 2 week delay in starting Cycle 2 or 3 due to non-hematologic toxicity will be removed from protocol treatment.

6.3 Dose Modifications for Docetaxel

Drug	Dose Level	Dose
Docetaxel	Full Dose	75 mg/m^2/d
Docetaxel	Dose Level –1	55 mg/m^2/d
Docetaxel	Dose Level –2	35 mg/m^2/d

NOTE: If treatment with docetaxel is delayed, atezolizumab dosing should be delayed as well and should resume to stay "in-sequence" with docetaxel cycles.

6.3.1 Hematologic adjustments

- Grade 3 febrile neutropenia should be retreated after recovery with a one level dose reduction.

- Grade 4 neutropenia lasting > 7 days should be retreated after recovery with a one level dose reduction.
- Grade 4 thrombocytopenia or thrombocytopenic bleeding should be retreated after recovery with a one level dose reduction.

6.3.2 Peripheral neuropathy adjustments

- Grade 2 = subsequent retreatment after recovery should be with a one level dose reduction.
- Grade 3 or higher peripheral neuropathy toxicity = discontinuation of study treatment.

6.3.3 Hypersensitivity reaction adjustments

- No dose reductions will be made for any hypersensitivity reactions. If, despite proper pretreatment with dexamethasone, the subject experiences a hypersensitivity reaction, treatment should be as indicated below:
    - Grade 1 symptoms (eg., mild flushing, rash, pruritis) = complete infusion. Supervise at bedside. No treatment required.
    - Grade 2 symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) = Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a slower rate, then increased incrementally to the initial planned rate. Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment and the rate of infusion should be decreased initially and then increased back to the recommended 1 hour infusion.
    - Grade 3 symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria) = Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The subject will go off study
    - Grade 4 symptoms = Anaphylaxis—Discontinue protocol treatment.

6.3.4 Hepatic adjustments

Subjects who develop abnormal liver function tests for any reason while on the study will have the following docetaxel dose reductions:

Abnormal Liver Function Dose Modifications for Docetaxel

Bilirubin	Alkaline Phosphatase	SGOT (AST)	Action
> ULN	or > 5 X ULN	or > 5 X ULN	Wait ≤2 weeks. If recovered*, reduce docetaxel dose by –1 dose level. If not, off study.

≤ ULN	and ≤ 5 X ULN	and 1.6-5 X ULN	Reduce docetaxel dose by –1 dose level.

*Bilirubin < ULN and alkaline phosphatase < 5 X ULN and SGOT (AST) < 5 X ULN.
NOTE: A maximum of two dose reductions per patient are allowed.
ULN= upper limit of normal for institution

6.3.5 Fluid retention adjustments:

- If symptomatic, subjects developing fluid retention may be treated with diuretics at the investigator's discretion.
- Grade 3 = Docetaxel should be held until resolution to < Grade 1, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.

6.3.6 Stomatitis adjustments:

Grade 3 or 4 stomatitis = retreatment after recovery to ≤ Grade 1 with a one level dose reduction.

6.3.7 Other non-hematologic toxicities:

- Grade > 3 AE = Docetaxel should be held until resolution to ≤ Grade 1 or less, then reinstituted, if medically appropriate, after recovery, with a one level dose reduction.
- Subjects requiring a > 2 week delay in starting Cycle 2 or 3 due to non-hematologic toxicity will be removed from protocol treatment.

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in Section 6.1, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances:

- Documented disease progression **NOTE:** patients who demonstrate clinical benefit per investigator's assessment may continue on atezolizumab treatment at the treating investigator's discretion. See Section 5 for additional detail.
- Site investigator determines a change of therapy would be in the best interest of the subject.
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant.
- Protocol therapy is interrupted for ≥ 6 weeks unless requiring steroid taper

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF). The subject will continue to be followed per Section 7.

6.5 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7 STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 21 days	Screening	On Treatment		Safety follow up visit[10]	Safety follow up evaluation[10]	Long-term Follow up[11]
	-28 days	Day 1 (± 3 days)	Day 8 (± 3 days)	30 days (± 7 days) post last dose	100 days (± 7 days) post last dose	(± 14 days)
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical History[1]	X					
Physical Exam	X	X		X		
Vital signs and ECOG Performance Status[2]	X	X		X		
AEs & concomitant medications	X	X		X	X	
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)[3]	X	X[3]	X	X		
Comprehensive Metabolic Profile (CMP)[3]	X	X[3]		X		
Thyroid Function (TSH, T4, T3)[4]	X	X[4]				
Pregnancy test (serum or urine) (WOCBP)[5]	X	X[5]				
DISEASE ASSESSMENT						
CT of chest[6]	X	X[6]				X[11]
CT or MRI of abdomen and pelvis[6]	X[6]	X[6]				X[11]
MRI Brain[6]	X	X[6]				X[11]
TREATMENT EXPOSURE[12]						
Atezolizumab		X				
Carboplatin, Gemcitabine **OR**		CARBO/GEM	GEM			
Docetaxel		DOCETAXEL				
SPECIMEN COLLECTION						
REQUIRED: Archival Tumor Tissue[7]	X					
OPTIONAL: Pre-Treatment Biopsy[8]		X[8]				
REQUIRED: Whole Blood, Serum, Plasma[9]		X[9]		X		
FOLLOW-UP						
Survival Status, Subsequent Therapy						X

Key to Footnotes

1: Medical History to include: smoking history, trial awareness question, diagnosis and staging (to include pathology report and Tumor Node Metastasis (TNM) staging) and prior treatment history.

2: Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status.

3: If screening CBC and CMP were performed within 7 days of Cycle 1 Day 1 of treatment, these do not need to be repeated. Day 8 CBC is applicable to only those subjects receiving gemcitabine. CBC with differential to include Hgb, Hct, WBC, ANC platelet count. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase.

4: Thyroid function to be checked at screening. During treatment, monitoring of thyroid function is at the site investigator's discretion- TSH, T3 and T4. Free versus total for T3 and T4 is at the site investigator's discretion.

5: Females of childbearing potential (FOCBP) must have a negative serum pregnancy test within 28 days prior to registration. FOCBP must also have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of atezolizumab then every 6 weeks during treatment.

6: Radiology Imaging: Screening tests should be done -28 days from registration. Pelvic CT or MRI should be done if it is a known disease site. MRI of brain should be performed at screening only if the site investigator suspects the presence of brain metastases. Tumor response assessment will consist of evaluation by CT scans of chest and abdomen (pelvis if known disease site) **every odd numbered cycle starting after screening with Cycle 3** (imaging selected for each subject should remain the same throughout the study). During follow up, tumor imaging is at the discretion of the investigator. Radiology imaging may take place within 7 days prior to a study visit.

7: REQUIRED IF AVAILABLE. Archival tumor tissue (prior to treatment with PD-1 or PD-L1 inhibitor) must be identified during the screening period and obtained prior to registration. Confirmation of acquisition should occur prior to C1D1 treatment. Sample requirement is FFPE block + 2 H&E stained slides or 17 unstained slides + 2 H&E stained slides. Sample will be used for PD-L1 status and genetic analyses. Subjects will be consented to optional storage of any remaining tumor samples after protocol-specified studies are complete. Stored samples will be reserved for future unspecified cancer-related research. See Correlative Laboratory Manual (CLM) for additional details.

8: OPTIONAL (RECOMMENDED). A biopsy after registration and prior to C1D1 treatment for PD-L1 status and other correlative studies should be from the primary tumor or a metastatic lesion. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient. Sample requirement is block + 2 H&E stained slides or 17 unstained slides and 2 H&E stained slides. Sample will be used for PD-L1 and genetic analyses. Subjects will be consented to optional storage of any remaining tumor samples after protocol-specified studies are complete. Stored samples will be reserved for future unspecified cancer-related research. See CLM for additional details.

9: REQUIRED: whole blood, serum, and plasma for cell-free DNA and proteomic correlative analysis. Obtain during screening or prior to treatment C1D1 and at time of progression/D30 safety visit. Subjects will be consented to optional storage of any remaining blood samples after protocol-specified studies are complete. Stored samples will be reserved for future unspecified cancer-related research. See CLM for additional details.

10: Safety follow-up visit should occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. A safety follow up call, email or other avenues as appropriate will be made 100 days (±7 days) after the last dose of study treatment for AE assessment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

11: Long Term Follow Up: Subjects will be followed every 6 months up to 18 months after the last patient is enrolled onto the study. Radiology imaging should be done at the site investigator's discretion during this time and results made available to the research staff. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

12: A cycle is equal to 21 days. All subjects will receive atezolizumab on Day 1. Chemotherapy is based on prior platinum therapy. If no prior platinum therapy: carboplatin (Day 1) and gemcitabine (Day 1 and 8). If prior platinum therapy: docetaxel (Day 1).

8 BIOSPECIMEN STUDIES AND PROCEDURES

For tumor specimens or blood collected in the protocol, please see the CLM for additional information regarding collection, labeling and shipping.

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-1 and anti-PD-L1 therapy.[22,38,39] In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of PD-1 or PD-L1 inhibitor, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Archival tumor tissue will be collected at baseline (REQUIRED, if available). Tumor tissue will also be collected by biopsy prior to C1D1 treatment (OPTIONAL) to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of PD-1 or PD-L1 inhibitors.

Blood samples will be collected at baseline (REQUIRED) and at the time of progression on study therapy to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T cell activation and lymphocyte subpopulations may provide evidence of biologic activity of PD-1 or PD-L1 inhibitors in humans. Correlations between these biomarkers and safety and efficacy endpoints may be explored in a future analysis to identify blood-based biomarkers that might predict which patients are more likely to benefit from PD-1 or PD-L1 inhibitors.

8.1 REQUIRED IF AVAILABLE: Archived Tumor Sample

Formalin-fixed, paraffin-embedded archival tumor tissue block for biomarker evaluation should be obtained (required if available) at screening for all subjects prior to C1D1 treatment. These biopsy samples should be from an excisional, incisional, punch or core needle biopsy. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. Sample requirement is FFPE block + 2 H&E stained slides or 17 unstained slides + 2 H&E stained slides. Sample should have been obtained prior to treatment with PD-1 or PD-L1 inhibitor.

8.1.1 PD-L1 Analysis

Specimens will be submitted for central PD-L1 immunohistochemistry (IHC) assessment. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed. PD-L1 expression will be evaluated on tumor cells and tumor-infiltrating immune cells with standard PD-L1 immunohistochemistry assay.

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Scoring will be performed for tumor cells expressing PD-L1 as a percentage of total tumor cells and tumor-infiltrating immune cells expressing PD-L1 as a percentage of tumor area, as previously described (tumor cells scored as percentage of PD-L1-expressing tumor cells: TC3≥50%, TC2≥5% and <50%, TC1≥1% and <5%, and TC0<1%; tumor infiltrating immune cells scored as percentage of tumor area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%).[40]

8.2 OPTIONAL (RECOMMENDED): Biopsy Prior to C1D1 treatment

A fresh or formalin-fixed, paraffin-embedded tumor tissue block or unstained slides of tumor sample (recent, after progression on **PD-1 or PD-L1 inhibitor** therapy) for biomarker evaluation is optional but if performed should be done prior to C1D1 treatment and received prior to C2D1. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. Sample requirement is FFPE block + 2 H&E stained slides or 17 unstained slides + 2 H&E stained slides.

Specimens will be submitted for central PD-L1 immunohistochemistry (IHC) assessment. These biopsy samples should be excisional, incisional, punch or core needle. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed. Please refer to section 8.1.1 for details regarding PD-L1 testing.

8.3 REQUIRED: Blood Draw Prior to C1D1 Treatment and at Progression

Whole blood, serum, and plasma will be collected prior to C1D1 and at the time of progression/D30 safety visit. Blood samples will be utilized for cell-free DNA and proteomic analysis by the sponsor-investigator to evaluate clonal evolution and mechanisms of resistance to therapy.

8.4 Storage of Biospecimens

Any remaining bio-specimens (tissue or blood) will be stored for future unspecified cancer related research once protocol described biospecimen-based studies are completed. Permission for storage will be obtained from subjects during informed consent.

8.5 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's sequence ID assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's sequence ID.

9. CRITERIA FOR DISEASE EVALUATION

9.2 RECIST 1.1 Criteria

Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (see Eisenhauer EA et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Can, 2009.45:p.228-247). Refer to the RECIST 1.1 publication for complete details on these criteria.

9.1.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.2 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.1.3 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. **NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.1.4 Target Lesions

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

9.1.5 Non-target Lesions

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

9.1.6 Evaluation of Target Lesions

NOTE: In addition to the information below, also see in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.1.7 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.1.8 Evaluation of Best Overall Response

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	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.2 Definitions for Response Evaluation – RECIST 1.1

9.2.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

9.2.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

9.2.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.2.4 Duration of Overall Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.2.5 Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.2.6 Clinical Benefit Rate

The clinical benefit rate is the proportion of all subjects with stable disease (SD) for at least 3 months, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.2.7 Progression Free Survival

A measurement from the date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.2.8 Overall Survival

Overall survival is defined by the date of treatment start to date of death from any cause.

9.3 Immune- Related RECIST Criteria

Immune-related RECIST criteria (see Bohnsack O. et al. Adaptation of the immune-related response criteria: irRECIST. ESMO 2014 Abstract 4958. http://www.irrecist.com/
Refer to the publication for complete details on these criteria.

9.3.1 Measurable lesion definitions and target lesion selection

Follow the definitions from RECIST 1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of:

- 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions
- 10 mm caliper measurement by clinical exam
- 20 mm by chest X-ray
- At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.
- Baseline: Target and Non-Target Lymph Node Lesion Definitions - Follow the definitions from RECIST 1.1
- Baseline: Bone Lesions- Follow the definitions from RECIST 1.1. Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.
- Baseline: Cystic and necrotic lesions as target lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

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

9.3.2 Follow-up

- Only index and measurable new lesions are taken into account. The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.
- Definition of Measurable New Lesions: In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.
- Non-Target Lesion Assessment- The RECIST 1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.
- New Non-Measurable Lesions Definition and Assessment: All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.

9.3.3 Best overall response using the irRECIST

The overall response according to the irRECIST is derived from time-point response assessments (based on tumor burden) as follows:

- Complete response (irCR) is defined by the complete disappearance of all lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
- Partial response (irPR) is defined by the decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. Stable disease (irSD) is when the measurements do not meet criteria for irCR or irPR, in absence of progressive disease (irPD).
- irPD is defined by a minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.

10 DRUG INFORMATION

10.1 Atezolizumab

Atezolizumab lacks the N-linked oligosaccharides typically observed on other CHO-derived monoclonal antibodies because it incorporates an amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of each heavy chain, resulting in a non-glycosylated antibody. This non-glycosylated antibody has minimal binding to Fcγ receptors and, consequently, prevents Fc-effector function and depletion of cells expressing PD-L1 at expected concentrations in humans.

	Early Phase I/II Material (F01)	Late Phase I/II and Phase III Material (F03)
Generic name	Atezolizumab	Atezolizumab
Code number	RO5541267/F01	RO5541267/F03
Chemical name	Humanized monoclonal antibody based on a human IgG1 framework containing heavy chain VHIII and light chain VκI subgroup sequences.	Humanized monoclonal antibody based on a human IgG1 framework containing heavy chain VHIII and light chain VκI subgroup sequences.
Chemical structure	The recombinant antibody consists of two heavy chains and two light chains with inter and intra chain disulfide bonds that are typical of IgG1 antibodies.	The recombinant antibody consists of two heavy chains and two light chains with inter and intra chain disulfide bonds that are typical of IgG1 antibodies.
Molecular weight	150 KD	150 KD
Description	Colorless to slightly yellow solution	Colorless to slightly yellow solution

10.1.1 Supplier/How Supplied

Atezolizumab Injection, 1200 mg/20 mL (60 mg/mL)

The atezolizumab Drug Product in Formulation F03 (late Phase I/II and Phase III clinical studies) is provided in a single-use, 20-mL 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 a solution containing histidine acetate, sucrose, and polysorbate 20 at pH 5.8.

GNE will supply atezolizumab at no charge to subjects participating in this clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Atezolizumab Injection, 1200 mg/20 mL (60 mg/mL)

Atezolizumab in Formulation F03 (1200 mg per vial) will be administered in 250-mL 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 μm in-line filters. The IV bag may be constructed of polyvinyl chloride or polyolefin, the IV infusion line may be constructed of polyvinyl chloride or polyethylene, and the 0.2 μm in-line filter may be constructed of polyethersulfone. The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. The dose solution should be stored at 2°C–25°C (36°F–77°F). The total storage time prior to administration should not exceed 8 hours.

10.1.3 Storage and Stability

Atezolizumab Injection, 1200 mg/20 mL (60 mg/mL)

Atezolizumab (F03) and the diluent must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. Atezolizumab and the diluent vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab Drug Product or the diluent; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light.

10.1.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

10.1.5 Dispensing

Atezolizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Atezolizumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

The most common side effects of atezolizumab are: Fatigue, decreased appetite, diarrhea, vomiting, arthralgia, asthenia, dyspnea, urinary tract infection, cough, pruritis, rash, nausea, fever and musculoskeletal pain. Please see current IB for a detailed list of side effects.

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events 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 that are considered potential adverse drug reactions associated with atezolizumab. There is also a potential for immune activation being associated with generalized systemic features (e.g., hypotension, respiratory failure, and other organ impairment).

Atezolizumab has been associated with risks such as the following: IRRs and immune−related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

10.2 Carboplatin

Please see package insert for detailed information regarding this medication

10.2.1 Other Names

Carboplatin (carboplatin for injection or platinum diamine [1,1-cyclobutane-decarbozxylate (2—0,0')-,(SP-4-2)])

10.2.2 Classification

Platinum compound chemotherapeutic agent

10.2.3 Mode of Action

Carboplatin is a second generation platinum compound and acts by covalently binding to DNA. It can react with 2 different sites on DNA to produce cross-links, either intra-stand (>90% of the time) or inter-strand (<5% of the time). Formation of DNA adducts results in inhibition of DNA synthesis and function as well as inhibition of transcription. Carboplatin can form complexes with nuclear and/or cytoplasmic proteins which may contribute to anti-tumor activity as well as toxicity.

10.2.4 Storage and Stability

Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30°C or 59-86°F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

10.2.5 Dose Specifics and Administration

All patients on protocol treatment will receive Carboplatin at AUC 4 IV infusion over 30-60 minutes, every 21 days for a total of 4 cycles. Carboplatin dosing is by the Calvert formula: Total Dose (mg) = (target AUC) x (CrCl+ 25).

10.2.6 Preparation

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL. Carboplatin solution can be further diluted to concentrations as low as 0.5 mg/mL with D5W or 0.9% normal saline.

Vial Size	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

10.2.7 Route of Administration
IV infusion.

10.2.8 Availability
Carboplatin is commercially available

10.2.9 Side Effects
Please see package insert for detailed information regarding side effects related to this drug.

Below are some common side effects related to Carboplatin.

Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common, but typically resolve by Day 28 when carboplatin is given as a single agent.

Allergic Reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.

Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.

Hepatic Toxicity: Elevated alkaline phosphatase, total bilirubin, and SGOT have been observed.

Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

10.3 Gemcitabine
Please see package insert for detailed information regarding this medication

10.3.1 Other Names
2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

10.3.2 Classification
Antimetabolite (nucleoside pyrimidine analogue)

10.3.3 Mode of Action
Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).

10.3.4 Storage and Stability
Unreconstituted drug vials are stored at controlled room temperature (15ºC to 30ºC, 59ºF to 86ºF). Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; as crystallization may occur. The unused portion should be discarded.

10.3.5 Preparation
Gemcitabine may be further diluted with normal saline as per institutional standards.

10.3.6 Route of Administration
IV infusion.

10.3.7 Availability
Gemcitabine is commercially available in 200 mg and 1 gm vials

10.3.8 Side Effects
Please see package insert for detailed information regarding side effects related to this drug.

Below are some common side effects related to Gemcitabine:
Neutropenia, anemia, thrombocytopenia, and leukopenia are reported. Rash with pruritis and injection-site reactions are can occur. Nausea and vomiting, diarrhea, constipation and mucositis have been reported. Abnormalities of hepatic transaminase enzymes occur in two-thirds of subjects, but they are usually mild, non-progressive, and rarely necessitate stopping treatment. Bronchospasm and/or dyspnea within a few hours of infusion of the drug, cough, rhinitis, pneumonitis may occur. Somnolence, insomnia, paresthesia, pain. Peripheral edema is reported

in about 30% of subjects. Flu-like symptoms are reported for about 20% of subjects. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia.

10.3 Docetaxel

Please refer to the latest version of the prescribing information that can be found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, and/or on the manufacturer's website.

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

10.3.1 Supplier/How Supplied

One-vial TAXOTERE (Injection Concentrate)

TAXOTERE Injection Concentrate is supplied in a single use vial as a sterile, pyrogen-free, non-aqueous solution.

TAXOTERE (docetaxel) Injection Concentrate 20 mg/1 mL: 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol. The vial is in a blister pack in one carton.

TAXOTERE (docetaxel) Injection Concentrate 80 mg/4 mL: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol. The vial is in a blister pack in one carton.

TAXOTERE (docetaxel) Injection Concentrate 160 mg/8 mL: 160 mg docetaxel in 8 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol. The vial is in a blister pack in one carton. Docetaxel (Taxotere) is commercially available and will not be supplied for this study.

10.3.2 Preparation

TAXOTERE Injection Concentrate (20 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw TAXOTERE from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate vials to stand at room temperature for approximately 5 minutes before use.
2. Using only a 21 gauge needle, aseptically withdraw the required amount of TAXOTERE injection concentrate (20 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.

If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.

3. Thoroughly mix the infusion by gentle manual rotation.
4. As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.
5. TAXOTERE infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

The TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions.

10.3.3 Storage and Stability

TAXOTERE final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. TAXOTERE final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration). In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36 and 46°F). Retain in the original package to protect from light. Freezing does not adversely affect the product.

10.3.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

10.3.5 Adverse Events

The most common side effects of TAXOTERE include:

- Changes in your sense of taste
- Feeling short of breath
- Constipation
- Decreased appetite
- Changes in your fingernails or toenails
- Swelling of your hands, face or feet
- Feeling weak or tired
- Joint and muscle pain
- Nausea and vomiting
- Diarrhea
- Mouth or lips sores
- Hair loss
- Rash
- Redness of the eye, excess tearing
- Skin reactions at the site of TAXOTERE administration such as increased skin pigmentation, redness, tenderness, swelling, warmth or dryness of the skin.
- Tissue damage if TAXOTERE leaks out of the vein into the tissues

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with urothelial carcinoma 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.
- Preexisting 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.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional

therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
    - Results in persistent or significant disability/incapacity(i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect defect in a neonate/infant born to a mother exposed to the IMP.
    - Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
    - Pregnancy
    - Overdose

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

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

Yes (definitive, probable, possible, unlikely)
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 subject's clinical state, inter-current 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 (unrelated)

Evidence exists that the AE has an etiology other than the Atezolizumab (e.g., preexisting medical condition, underlying disease, inter-current 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 Atezolizumab.

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

11.1.5 AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product. AESIs shall be forwarded to Genentech/Roche **within fifteen (15) calendar days** of the awareness date.

The Atezolizumab Events of Special Interest

Adverse events of special interest for this study include the following:

- 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:
    - Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
    - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by Atezolizumab, 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 the study drug is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, macrophage activating syndrome and hemophagocytic lymphohistiocytosis .
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 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)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Reporting Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to Genentech (GNE)

HCRN will report all SAEs to GNE **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to GNE as it is received from site.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the Genentech's parent IND at the time of submission. Additionally, All written IND Safety Reports submitted to the FDA by HCRN on behalf of the sponsor-investigator must also be faxed to Genentech/Roche Drug Safety: Fax: (650) 225-4682 or (650) 225-4630.

HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, HCRN will submit a copy of these reports to GNE at the time of submission to FDA.

11.5 IND Safety Reports Unrelated to this Trial

GNE will provide IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

General Considerations: Statistical analysis of this study will be the responsibility of Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Cancer Center (IUSCC). Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Missing data will not be imputed. Data analysis will be performed in SAS.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature of the protocol; however, all changes from the original analysis plan will be documented in the final study report. The statistical analysis methods are outline below.

12.1 Study Design

This is a single-arm phase II study of immunotherapy with atezolizumab plus addition of chemotherapy (carboplatin+gemcitabine or docetaxel) in patients with cisplatin-ineligible urothelial carcinoma previously treated with PD-1 or PD-L1 inhibitor.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

The primary endpoint is PFS assessed by RECIST 1.1 and is defined as the time from date of treatment start until the criteria for disease progression is met as defined by RECIST 1.1 criteria or death as a result of any cause; in the absence of an event, the endpoint will be right-censored at the date of last disease assessment (see also section 9.2.8).

12.2.2 Definition of Secondary Endpoints

- Toxicity assessed by CTCAE Version 4.03.
- ORR (CR+PR) assessed via RECIST 1.1 (Section 9.2.5)
- ORR (iCR+iPR) assessed via irRECIST (Section 9.3.3)
- CBR (CR+PR+SD > 3 months) assessed via RECIST 1.1 (Section 9.2.6)
- CBR (iCR+iPR+iSD > 3 months) assessed via irRECIST (Section 9.3.3)
- PFS assessed by irRECIST defined as the time from date of treatment start until the criteria for disease progression is met as defined by irRECIST criteria or death as a result of any cause; in the absence of an event, the endpoint will be right-censored at the date of last disease assessment.
- OS defined by the date of treatment start to date of death from any cause

12.3 Sample Size and Accrual

In historical data, the median PFS among patients who received chemotherapy in the 2nd or 3rd line setting in metastatic urothelial carcinoma is around 4 months.[41-46] Therefore, for this study we will consider the historical control for 2nd line carboplatin + gemcitabine or 3rd line Docetaxel in metastatic urothelial carcinoma to be 4 months. To be further conservative, we will include analysis of a virtual control arm as an exploratory endpoint to analyze real-life data from patients receiving atezolizumab as first-line and then receive carboplatin + gemcitabine in the 2nd line setting. We are using the virtual control arm for this purpose because historical data in this particular setting is not available to date.

The primary goal is to estimate PFS among patients to be treated with atezolizumab in combination with carboplatin + gemcitabine or docetaxel, who have cisplatin-ineligible metastatic urothelial carcinoma and who have progressed on prior PD-1 or PD-L1 inhibitor. We hypothesize that patients receiving atezolizumab plus chemotherapy (carboplatin + gemcitabine or docetaxel) will have a median PFS of 0.6 year (7.2 months). Under the exponential distribution assumption, this corresponds to an annual hazard rate of 1.155. The number of events is 30 required to obtain a 95% confidence interval of [0.79, 1.60] for estimating the hazard rate. Of note, the historical data suggest a median PFS of 4 months, which corresponds to a hazard rate of 2.08, well outside the anticipated 95% CI. An event is defined as a patient with progression or death. Assuming an accrual period of 24 months (1.375 per month) and maximum follow-up of 18 months after the last patient is enrolled, an accrual of 33 is expected to yield 30

events. To allow for replacement of patients who are not evaluable for efficacy (estimated to be 10%), up to 37 patients will be enrolled.

12.4 Assessment of Safety

Safety will be assessed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.03). Please refer to the Study Calendar for the schedule of toxicity assessment. The safety population will comprise all subjects who receive at least one dose of trial drug(s)

12.5 Assessment of Efficacy

The analysis of PFS and other efficacy endpoints will use the efficacy population. This will comprise all subjects who receive at least one dose of trial treatment (atezolizumab plus carboplatin + gemcitabine or docetaxel) and either undergo at least one post-baseline assessment or die before any evaluation.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

The PFS along with 95% CI will be estimated using the Kaplan-Meier method in the Efficacy population.

12.6.2 Analysis Plans for Secondary Objectives

In the Efficacy population, median PFS by irRECIST will be estimated and tested similarly to the primary endpoint. Objective response rate and clinical benefit rate will be estimated with two-sided 95% exact binomial confidence intervals. OS will be estimated using Kaplan-Meier methodology. Toxicities will be tabulated in the Safety population.

To compare PFS with the historical control,

- Null hypothesis – Patients receiving atezolizumab plus chemotherapy (carboplatin + gemcitabine or docetaxel) will have a median PFS of 4 months.
- Alternative hypothesis – Patients receiving atezolizumab plus chemotherapy (carboplatin + gemcitabine or docetaxel) will have a median PFS of 7.2 months.

With 1 sided alpha level of 0.1, the sample size of 33 will have 81.4% power to detect the hypothesized difference in median PFS, assuming an accrual period of approximately 24 months (1-2 per month) and maximum follow-up of 18 months after the last patient is enrolled. The power calculation is based the SWOG calculator “One Arm Nonparametric Survival Sample Size and Power”, based on the assumptions of uniform accrual over time, no loss to follow-up, exponentially distributed death times. As noted in Section 12.3, to allow for replacement of patients who are not evaluable for efficacy (estimated to be 10%), up to 37 patients will be enrolled.

12.6.3 Analysis Plans for Exploratory Objectives

An exploratory analysis will compare OS in the Efficacy population of this study to the virtual control arm (per section 2.2.4) using a stratified log-rank test. Kaplan-Meier plots will also be generated with two-sided 90% confidence intervals for estimated median OS.

In the Efficacy population, % of PDL-1 cells positive in the tumors at baseline and at time of progression on PD-1 or PD-L1 inhibitor will be compared using paired t-tests. For markers of checkpoint efficacy or resistance (positive or negative) and PDL-1 status, frequencies at each time point will be reported, and changes over time will be assessed with McNemar's tests.

12.6.4 Other Planned Analyses

For the Enrolled population, descriptive statistics will be used the characterize subject demographic and clinical characteristics, disposition, and significant protocol violations. In the safety population, concomitant medications and exposure will be described.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted in accordance with the Indiana University Melvin and Bren Simon Cancer Center's (IUSCC) DSMP for High Risk Phase II Trials.

HCRN facilitated oversight activities for High Risk Phase II Trials include:

- Review and processing of all AEs requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator, including a weekly update of aggregate AE data. For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the sponsor investigator will notify HCRN, who will notify the DSMC Chair and Compliance Officer immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
- Notify participating sites of adverse events potentially requiring expedited. reporting and subsequent DSMC recommendations for study modifications.
- Investigators will conduct continuous review of data and patient safety.
- Coordinate *monthly* (Phase II) meetings which will include each accruing site.
    - These meetings should include review of data, the number of subjects and significant toxicities as described in the protocol. HCRN should maintain meeting minutes and attendance for submission to the DSMC upon request.
- Conduct the trial across all participating sites in accordance with the requirements set forth in the IUSCC DSMP.

13.2 IUSCC Data Safety Monitoring Committee Oversight

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study to assess toxicity, compliance, data integrity, and accrual per the Institutional DSMP. Trials managed by HCRN are not routinely audited or monitored by IUSCC; however, the IUSCC DSMC retains the right to audit HCRN trials on a for cause basis.

The IUSCC DSMC will review study data semi-annually during the active treatment and safety follow-up portion of the trial per the IUSCC DSMP.

In preparation for the IUSCC DSMC review, HCRN will provide the following:

- Monthly Summary Reports
- Reports of the following, if not already included in the Monthly Summary Report:
    - Adverse event summary report (including serious adverse events)
    - Study accrual patterns
    - Protocol deviations
- Audit and/or monitoring results, if applicable
- HCRN month study update meeting minutes/ attendance

Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. The IUSCC DSMC will notify the sponsor-investigator and other regulatory bodies, as appropriate, for issues of immediate concern. The sponsor-investigator will work with HCRN to address the DSMC's concerns as appropriate.

At any time during the conduct of the trial, if it is the opinion of the sponsor-investigator that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC Chair and Compliance Officer. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the investigator reports.

13.2.1 IND Annual Reports

Since this study has an IND held locally by the IU principal investigator, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site. Corrections will be made by the study site personnel.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause audits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by GNE or its designee as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Office for this trial. Data will be collected through a web based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on

secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, GNE, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

14.5 Aggregate Reports

The sponsor-investigator (Nabil Adra) will forward a copy of the Final Study Report to Genentech/Roche upon completion of the study.

14.6 Study Close-out

Any study report submitted to the FDA by the sponsor-investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Atezolizumab IIS Clinical Operations
Email: anti-pdl-1-mpd3280a-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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APPENDIX 1: MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.

Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as a Grade 3 or 4 event
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator.

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab.–Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. c
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable

Event	Management
	on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate).

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).

Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in 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, should be treated according to the guidelines below.

Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 2-4	• Permanently discontinue atezolizumab and contact sponsor-investigator. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to re-challenge patients should be based on the investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Sponsor-investigator is available to advise as needed.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release cyndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction [29]. CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 [30, 31], including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or**	• Immediately interrupt atezolizumab infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage

Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever b with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator. • Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after considering the benefit-risk ratio.
g. Refer to Riegler et al. [32] for information on experimental treatments for CRS.

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management	
Amylase and/or lipase elevation, Grade 1	• Continue atezolizumab • Monitor amylase and lipase prior to dosing	
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5-2.0 x ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone.	**Asymptomatic with amylase and/or lipase > 2.0-5.0 x ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]	
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]	
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.	

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length

Event	Management

of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

DERMATOLOGIC EVENTS

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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1−2 mg/kg/day if event does not improve within 48−72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies.

Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-RELATED MENINGOENCEPHALITIS

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines below.

Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

IMMUNE-RELATED NEPHRITIS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. a • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.

a. Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor-investigator.
b. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor-investigator.

IMMUNE-RELATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine-kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle-biopsy. One etiology of myositis is immune-mediated, which is the current concern with atezolizumab.

It is recommended that atezolizumab should be withheld for moderate or severe (Grade 2 or 3) immune-related myositis and permanently discontinued for recurrent severe or life-threatening myositis (recurrent Grade 3 and Grade 4). Please refer the patient to rheumatologist and/or neurologist and consider muscle biopsy and supportive measures as clinically indicated. Corticosteroids treatment with 1-2 mg/kg/day IV methylprednisolone or higher-dose bolus if severely compromised (weakness severely limiting mobility, cardiac function, respiratory function, dysphagia) and/or additional immunosuppressive agents should be administered for ≥ Grade 2 events or if the event does not improve after initial corticosteroids. Please refer to the table below for detailed management guidelines for immune-mediated myositis.

Management Guidelines for Immune-Related Myositis

Event	Management
Immune-related myositis, Grade 1	• Continue atezolizumab • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines
Immune-related myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact site investigator. • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Consider treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor-investigator. [c]
Immune-related myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact site investigator.

	• Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact HCRN. [c] • For recurrent events, treat as a Grade 4 event
Immune-related myositis, Grade 4	• Permanently discontinue atezolizumab and contact site investigator.[c] • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone or higher dose bolus if subject is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

IV, intravenous

[a] Atezolizumab may be withheld for a period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor-investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor-investigator.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/L (100,000/μL)
  - ANC < 1.0×10^9/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 1.

Table 1 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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