# A Multi-institutional Phase II Study to Evaluate Efficacy and Safety of TAlazoparib, Radiotherapy and Atezolizumab in gBRCA 1/2 negative Patients with PD-L1+ Metastatic Triple Negative Breast Cancer (TARA)

**Sponsor Investigator**
Mylin A. Torres, MD
Co-Leader Cancer Prevention and Control Program
Winship Cancer Institute
Professor
Department of Radiation Oncology
Emory University School of Medicine
Email: matorre@emory.edu

**Co-Investigators**

Manali Bhave, MD
Assistant Professor
Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine
Manali.ajay.bhave@emory.edu

David Schuster, MD
Director
Division of Nuclear Medicine and Molecular Imaging
Professor
Department of Radiology and Imaging Sciences
Emory University Atlanta, GA
Email: dschust@emory.edu

**Statistician**
Jeffery Switchenko, PhD
Biostatistics & Bioinformatics Shared Resource at Winship Cancer Institute
Department of Biostatistics & Bioinformatics, Emory University
1518 Clifton Road/Atlanta, Georgia 30322
Email: jswitch@emory.edu

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## PROTOCOL SIGNATURE PAGE

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**VERSION DATE:** 10AUG2022

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

_____

Site Investigator Name (printed)

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Site Investigator Title

_____

Name of Facility

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Location of Facility (City and State)

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# SYNOPSIS

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| **TITLE** | A Multi-institutional Phase II Study to Evaluate Efficacy and Safety of TAlazoparib, Radiotherapy and Atezolizumab in gBRCA 1/2 negative Patients with PD-L1+ Metastatic Triple Negative Breast Cancer (TARA) |
| **SHORT TITLE** | Study to Evaluate Efficacy and Safety of TAlazoparib, Radiotherapy and Atezolizumab in gBRCA 1/2 negative Patients with PD-L1+ Metastatic Triple Negative Breast Cancer |
| **PHASE** | 2 |
| **OBJECTIVES** | **Primary Objective**<br>Estimate objective response rate (ORR) of talazoparib, high dose radiotherapy and atezolizumab, eight weeks after the first dose of atezolizumab in non-irradiated lesions of gBRCA1/2 pathogenic variant negative mTNBC patients whose tumors are PD-L1 immune cell (IC)-positive.<br><br>**Secondary Objectives**<br>• Determine the frequency and severity of adverse events using CTCAE v 5.0 after induction talazoparib followed by concurrent talazoparib, high dose radiation, and atezolizumab given as second or third-line treatment for PD-L1 positive metastatic triple negative breast cancer (mTNBC) (≥ 2 lesions)<br>• Obtain progression free survival (PFS) data in gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, radiation, and atezolizumab<br>• Obtain overall survival (OS) data in gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, radiation, and atezolizumab<br>• Determine ORR by immune-related RECIST (irRECIST)<br>• Determine duration of overall response (DOR) to talazoparib, high dose radiation, and atezolizumab given in the second or third-line setting to BRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate<br>• Determine disease control rate (DCR) in gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, high dose radiation, and atezolizumab given in the second or third-line setting<br>• Determine time to progression (TTP) in gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, high dose radiation, and atezolizumab given in the second or third-line setting |

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| | • Determine adherence to prescribed talazoparib, high dose radiation, and atezolizumab in the second or third-line setting among PD-L1 positive mTNBC patients<br>• Determine best overall tumor response to talazoparib, high dose radiation, and atezolizumab in the second or third-line setting among PD-L1 positive mTNBC patients |
| **STUDY DESIGN** | This is a Phase II study designed to assess efficacy and safety of talazoparib, high dose radiation, and atezolizumab in gBRCA 1/2 negative patients with metastatic TNBC that is PD-L1 positive. A total of 23 subjects will be enrolled. A safety lead in of 6 patients will be performed. All patients will be treated with induction talazoparib of 1mg PO daily starting Day 1. Patients will then receive 8 Gy x 3 QOD of radiation to 1-4 extracranial lesions starting Day 12, 13 or 14. 840 mg of atezolizumab intravenously (IV) will be given ~ Day 15 of the 1st cycle and then on Day 1 and Day 15 of the remaining cycles. Each cycle equals 28 days. Treatment will continue until progression or severe toxicity. |
| **KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)** | 1. Biopsy proven metastatic triple negative breast cancer (estrogen receptor (≤/=10%), progesterone receptor (≤/=10%) and no overexpression of HER2 as evaluated by local institutions with at least 2 extracranial metastatic lesions on imaging.<br>2. PD-L1 positive tumor infiltrate as defined as ≥1% on IHC using the SP142 Ventana Assay.<br>3. Known gBRCA status (only gBRCA pathogenic variant negative patients are eligible).<br>4. Patients must have at least 1 extracranial metastatic lesion (may be measurable or non-measurable disease by RECIST v 1.1) that is amenable to high dose radiotherapy and at least one additional extracranial lesion of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) that will not receive radiotherapy on this study. Of note, lesions may be in the same organ but must be 2 cm apart.<br>5. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1)<br>6. Patients must have received at least one and no more than three previous lines of chemotherapy treatment in the advanced setting with or without immune therapy. Patients with disease recurrence or progression following neoadjuvant or adjuvant cytotoxic chemotherapy are not eligible unless they have received at least one line of chemotherapy with or without immune therapy in the advanced setting. NOTE: Targeted small molecules (e.g. tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (e.g. bevacizumab, afilbercept) are not counted in the number |

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| | of lines of therapy. Cytotoxic chemotherapy with or without immune therapy for advanced disease prior to protocol treatment is not permitted within 2 weeks of the protocol treatment. Patients may or may not have received radiotherapy or neoadjuvant or adjuvant chemotherapy in the treatment of their initial, non-metastatic breast cancer or metastatic breast cancer, but must be entered on study 2 weeks after their last dose of radiotherapy, last cycle of chemotherapy and biologic therapy (if applicable) for mTNBC and have sufficient resolution of side effects per physician assessment at time of talazoparib.<br>7. Patients must be eligible for radiotherapy, talazoparib, and atezolizumab.<br>8. Demonstrate adequate organ function within 14 days prior to registration.<br>9. No evidence of progression of breast cancer within the first 3 months of prior immune therapy for non-metastatic or metastatic breast cancer. |
| **STATISTICAL CONSIDERATIONS** | Sample size is determined using Simon's 2-stage Minimax design to detect a 20% increase in objective response rate (ORR). The null hypothesis that the true response rate among gBRCA1/2 negative patients of 10%, based on the TOPACIO study[25], will be tested against a one-sided alternative. In the first stage, 7 patients will be accrued. If there are 0 responses in these 7 gBRCA1/2 negative patients, the study will be stopped. Otherwise, 11 additional patients will be accrued for a total of 18 evaluable patients. This design yields a Type I error rate of 0.1 for one sided test and power of 80% when the true response rate is 30% in the gBRCA negative patients. Assuming an attrition rate of 20%, we will enroll 23 total patients **without gBRCA 1/2 pathogenic variants**. |
| **TOTAL NUMBER OF SUBJECTS** | N = 18 evaluable subjects: 23 total patients accounting for dropout accounting for drop out |
| **ESTIMATED ENROLLMENT PERIOD** | Estimated 27 months from time of lead site opening |
| **ESTIMATED STUDY DURATION** | Estimated 36 months |

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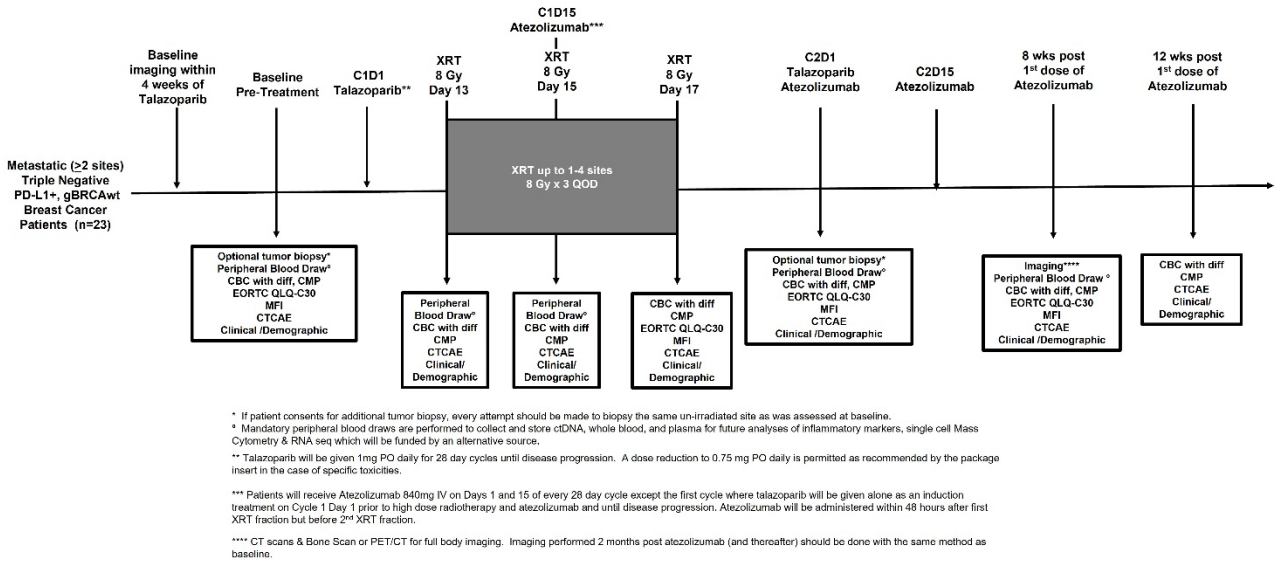
## SCHEMA




* If patient consents for additional tumor biopsy, every attempt should be made to biopsy the same un-irradiated site as was assessed at baseline.
^ Mandatory peripheral blood draws are performed to collect and store ctDNA, whole blood, and plasma for future analyses of inflammatory markers, single cell Mass Cytometry & RNA seq which will be funded by an alternative source.

** Talazoparib will be given 1mg PO daily for 28 day cycles until disease progression. A dose reduction to 0.75 mg PO daily is permitted as recommended by the package insert in the case of specific toxicities.

*** Patients will receive Atezolizumab 840mg IV on Days 1 and 15 of every 28 day cycle except the first cycle where talazoparib will be given alone as an induction treatment on Cycle 1 Day 1 prior to high dose radiotherapy and atezolizumab and until disease progression. Atezolizumab will be administered within 48 hours after first XRT fraction but before 2nd XRT fraction.

**** CT scans & Bone Scan or PET/CT for full body imaging. Imaging performed 2 months post atezolizumab (and thereafter) should be done with the same method as baseline.

ctDNA – circulating tumor DNA; CBC with diff – complete blood cell count with differential; CMP – complete metabolic panel; CTCAE – National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; Mets - metastasis;
MFI – Multidimensional fatigue Inventory; EORTC QLQ-C30 - EORTC Quality of Life Questionnaire Core 30; gBRCA1/2 negative – germline BRCA 1/2 pathogenic variant negative, e.g. germline BRCA1/2 wildtype or gBRCA variants of uncertain significance; XRT-radiotherapy

To participate on this study, patients must fulfill all eligibility criteria and must not meet any exclusion criteria, as well as consent to blood draws and resulting biospecimen collection and analysis. Archival tissue collection for research purpose before treatment is optional but encouraged. Fresh tumor tissue collection from the same non-irradiated site for research purposes before and after first dose of atezolizumab (prior to C1D1 and C2D1) is also optional but encouraged. gBRCA and PD-L1 status must be confirmed prior to treatment.

# 1. BACKGROUND AND RATIONALE

## 1.1 Background and Rationale

Metastatic breast cancer is an incurable disease. While the discovery of agents which specifically target hormone receptor and Her2 positive tumors have significantly improved outcomes in patients with these breast cancer subtypes, the lack of a clearly defined therapeutic target in women with metastatic triple negative breast cancer (mTNBC) results in patients continuing to do poorly with a median survival of 18 months or less.[1] A higher proportion of TNBCs are diagnosed in younger women, BRCA1 carriers and/or women of African or Hispanic ancestry. Among all breast cancer subtypes, TNBC has the greatest potential to benefit from immune therapy, as it is associated with more immunogenicity than non-TNBCs.[2,3] Enhanced immune activity characterized by tumor infiltrating lymphocytes in the biopsy and surgical specimens of TNBC patients is associated with overall improved prognosis.[4] Therefore, therapies aimed at augmenting the immune response to TNBC may address the need for more tumor specific and less toxic treatment.

Higher genetic instability, enhanced mutational load, appearance of neoantigens and the expression of programmed death ligand 1 (PD-L1) seen in tumor-infiltrating immune cells of patients with TNBC suggests that checkpoint inhibition of PD-L1 may be a beneficial treatment strategy in this breast cancer subtype.[5,6] Atezolizumab, an antibody which specifically targets PD-L1 on tumor cells, was efficacious in TNBC based on results from the IMpassion 130 Phase III trial. Among all patients, overall response rates (ORR) at 8 weeks were significantly higher in mTNBC patients treated with nab-paclitaxel and atezolizumab vs. nab-paclitaxel and placebo (56% vs. 49.5%, respectively, p=0.002). In patients with PD-L1 positive tumors (41% of patients), the difference in ORR rates was even higher (58.9% with atezolizumab vs. 42.6% placebo, p=0.002) and correlated with a significantly improved median progression-free survival of 7.2 months vs. 5.5 months with nab-paclitaxel alone (p=0.002) and clinically, meaningful improvement of overall survival of 7 months.[7,8] Atezolizumab, importantly, did not compromise patient reported health related quality of life, as assessed by EORTC QLQ-C30.[7,9,10]

Nevertheless, in spite of these advances, prognosis for mTNBC patients treated with atezolizumab and nab-paclitaxel remains poor as patients ultimately progress within a relatively short time period. Among gBRCA1 or gBRCA2 mutation carriers (5-10% of all breast cancer patients), PARP inhibitors [PARPi(s)], including talazoparib, are approved in PD-L1 negative mTNBC and are commonly prescribed as subsequent treatment in gBRCA positive patients with PD-L1 positive tumors who progress on atezolizumab and nab-paclitaxel.[11] However, in PD-L1+ mTNBC patients who are not gBRCA carriers, median duration of response is only 8.5 months after treatment with atezolizumab, and cytotoxic chemotherapy, a highly indiscriminate treatment, remains the primary therapy for progressive disease and is associated with significant toxicity often without durable long-term benefit in the majority of patients.[7] Indeed, among patients on IMpassion130 who resumed anticancer treatment after developing progressive disease on atezolizumab and nab-paclitaxel, over 95% were treated with other chemotherapy agents while less than 4% received additional immune therapy.[7] A potential, alternative therapeutic strategy would be to introduce agents which re-sensitize the immune system to atezolizumab and promote a more durable tumor-specific response that spares patients from toxicities associated with traditional chemotherapy regimens.

Additionally, there remain many mTNBC patients who were treated with chemotherapeutic agents and/or other immune therapies (e.g. pembrolizumab) in the first line setting, and these patients have not received PD-L1 checkpoint blockade despite having PD-L1+ tumors. Therefore, it is possible that these heavily pre-treated PD-L1+ mTNBC patients who are naïve to atezolizumab may still benefit from an atezolizumab combination in the second line setting or beyond. It is also possible that sensitivity to atezolizumab may be restored in mTNBC patients previously treated with this agent as noted above.

PARPi(s) are one option for increasing response to atezolizumab in heavily pretreated (with or without previous immune therapy) mTNBC PD-L1+ patients, as preclinical models have demonstrated moderately enhanced antitumor activity when both agents are combined, irrespective of gBRCA mutation status (see below). Among PARPi(s) used in breast cancer, talazoparib is the most potent in preclinical studies. It not only has strong catalytic inhibition, but it also traps PARP at levels 100-fold higher than other PARPi(s).[12,13] Talazoparib, therefore, is an attractive PARPi to be used in combination with atezolizumab, a drug with proven efficacy in mTNBC patients with PD-L1+ infiltrate. Talazoparib has already been studied with avelumab, another PD-L1 inhibitor, in small Phase I studies, without dose reductions or concerning toxicities and modest to moderate activity in mTNBC patients but no study has examined the use of talazoparib with atezolizumab specifically.[14] Moreover, PARPi(s) are known radiosensitizing agents even in the absence of BRCA mutations. Therefore, it is possible that within the context of atezolizumab, radiation may elicit an abscopal response, particularly when combined with talazoparib, the most potent PARPi in its class. We, therefore, hypothesize that talazoparib and radiation in combination with atezolizumab will improve upon the modest activity noted with talazoparib and avelumab even in patients without gBRCA pathogenic variants. It is thus possible that the combination of all three agents will elicit a stronger antitumor response than any of these agents given alone to gBRCA1/2 negative patients. However, these three agents have not been tested previously in PD-L1+ mTNBC patients with or without gBRCA pathogenic variants. Therefore, we propose a Phase II study evaluating the efficacy and safety of talazoparib given with high dose radiation and atezolizumab to restore sensitivity to immune therapy in, gBRCA1/2 negative mTNBC PD-L1+ patients, who develop progressive disease on atezolizumab or in patients who have progressed on chemotherapy with or without immune therapy in the first or second line. This will allow us to not only assess the safety of this strategy in these patients but also assess the potential ability of talazoparib coupled with radiation to amplify the immune response in heavily pretreated (with or without immune therapy) patients with PD-L1+ mTNBC tumors.[7] An advantage of this approach is the use of talazoparib to enhance local treatment (radiotherapy) to improve systemic response to immune therapy without increasing the risk for widespread side effects associated with the addition of other experimental or traditional systemic cytotoxic agents which circulate throughout the body.

## 1.2 PARP Inhibitors and Radiotherapy

Talazoparib is the most potent of all PARPi(s), a class of drugs which enrich unrepaired DNA damage, and are therefore, potential radiosensitizers that promote apoptosis. PARPi(s) suppress homologous recombination and PARP-1-dependent nonhomologous end joining (NHEJ) repair while promoting error-prone alt-NHEJ and can induce "synthetic lethality" in cancers with underlying DNA damage repair abnormalities, such as patients with gBRCA1/2 mutations. Although PARPi (s) are approved for use in gBRCA mutation carriers, there is also noted activity in tumors with somatic DNA repair pathway mutations (e.g. homologous recombination deficiency [HRD]) which have been reported in up to 60% of TNBCs.[15] In addition, previous pre-clinical and clinical studies have indicated that PARPi(s) are an effective radiosensitizer irrespective of gBRCA status, as PARP inhibition may synergize with the single- and double-stranded DNA breaks induced by radiotherapy.[16-18] Most clinical studies have given 1-2 weeks of induction PARPi therapy before concurrent treatment with radiation. Studies, like ours, examining the use of focused high-dose radiation (as opposed to large field irradiation) with a PARPi have the potential to increase tumor response without exacerbating hematologic toxicities typically associated with PARPi alone [Grade 3 anemia (38%), neutropenia (18%), and thrombocytopenia (11%)].[11] Pertinent to immune therapy, both PARPi(s) and radiotherapy upregulate the expression and secretion of chemokines such as CCL2, CCL5, CSCL-16, and CSCL-10 and promote intratumor infiltration by cytotoxic T lymphocytes.[19,20] These two treatments also independently upregulate PD-L1 on the tumor cell surface. Therefore, talazoparib and radiotherapy given concurrently have the potential to amplify tumor responses to PD-L1 immunotherapies like atezolizumab, regardless of gBRCA status.[21,22]

## 1.3 PARP Inhibitors and Immune therapy

PARPi(s) impair repair of nucleotides and base excision which generate cytosolic DNA fragments that activate the DNA-sensing cGAS-STING pathway leading to production of type I interferon and antitumor activity regardless of BRCAness within the tumor.[23] Furthermore, genomic instability resulting from PARPi yields many protein altering mutations that create immunogenic neo-antigens independent of BRCA1/2 status.[21,23] Moreover, BRCA1/2 status has no bearing on the increased expression of PD-L1 secondary to PARPi treatment observed in breast cancer cell lines and animal models.[21] Therefore, there is mechanistic rationale for combining PARPi with immune therapy in patients who are not gBRCA mutation carriers. Evidence in support of this treatment approach comes from single-arm Phase 1 and 2 Trials conducted in patients with recurrent platinum-resistant ovarian cancer.[24] In these studies, the combination of niraparib, a PARPi, and pembrolizumab, a PD-1 inhibitor, was tolerable and demonstrated promising responses in patients without BRCA mutations.[24] Additional studies exploring this combination of drugs in mTNBC patients without BRCA mutations are also ongoing. In the Phase 1b/2 Javelin PARP Medley study, talazoparib (1mg PO daily) is given concurrently with the PD-L1 inhibitor, avelumab (800mg Q2 weeks). This regimen has demonstrated a modest response rate of 18.2% with an acceptable safety profile in heavily chemotherapy pre-treated mTNBC patients who are naïve to PARPi and/or immune therapies.[14] Notably, higher response rates were seen in tumors with DNA damage repair pathway mutations. Importantly, concurrent talazoparib and avelumab had a similar safety profile to either avelumab or talazoparib given as monotherapies. Treatment related Grade 3 or higher adverse events, predominantly anemia, thrombocytopenia, or neutropenia, were successfully managed by either reducing the talazoparib dose to 0.75mg daily or dose interruption of both avelumab and

talazaporib.[14] Dose reductions were necessary in a small minority of patients, and thus provide support for talazoparib 1mg daily dosing with atezolizumab in our proposed study.

In another single arm, Phase 2 TOPACIO/KEYNOTE-162 study, niraparib used in combination with pembrolizumab also showed promising response rates and an acceptable safety profile in patients with mTNBC.[25] Among 27 patients with BRCA wild-type tumors (tBRCAwt), the ORR was 11%, while among 15 patients with BRCA tumor mutations, the ORR was 47%. Among tBRCAwt patients (n=27), 5 with mutations in the homologous recombination repair pathway had a higher ORR of 20%.[25] Patients with PD-L1 positive disease had an ORR of 32%, independent of BRCA tumor status, indicating that this particular subset of patients may be more responsive to the combination of PARPi and immune therapy. It is important to note, however, that PD-L1 positivity was higher in the tBRCAmut population (80%) compared to the tBRCAwt population (56%).[25] Similar to the Javelin study, the most common grade 3 or higher adverse events were anemia (18%), thrombocytopenia (15%) and fatigue (7%).[25] Two patients developed Grade 3 immune-related adverse events, which resolved after treatment with corticosteroids and interruption of niraparib or interruption/discontinuation of pembrolizumab.[25] Findings from these studies indicate efficacy in patients with mTNBC PD-L1 positive disease previously treated with chemotherapy and independent of BRCA status as well as acceptable rates of toxicity and thus support further exploration of PARPi with immune therapy, particularly in the context of high dose radiotherapy. Indeed, given that radiation was not a component of treatment in any of the above studies, it is possible that higher response rates may be seen by the addition of this local therapy (see below). As atezolizumab has already demonstrated activity in mTNBC patients with PD-L1 positive infiltrate, we propose combining talazoparib with high dose radiation and atezolizumab, specifically, in PD-L1+, mTNBC patients without gBRCA pathogenic variants.

### 1.4 Radiotherapy and Immune Therapy

A number of both preclinical studies and clinical trials in a variety of cancers have shown promising synergism between radiotherapy and immune therapy leading to enhanced treatment efficacy. Concurrent administration of anti-PD-L1 antibodies with radiotherapy in murine models increases CD8+ T cell responses associated with improved local tumor control.[26] Preclinical evidence indicates that at least part of the clinical effectiveness of radiation is due to its ability to induce local cell death with a release of immunogenic factors termed “immunogenic cell death.” Ionizing radiation-mediated tumor regression is dependent on the adapter protein STING for type I interferon-dependent antitumor effects of radiation.[27] This allows for mobilization of several host immune effector mechanisms that stimulate anti-tumor immune activity. There are several immune effector mechanisms that have been described in the literature including the creation of an inflammatory microenvironment characterized by the release of tumor antigens and danger-associated molecular patterns including calreticulin, ATP and high-mobility group protein B1 (HMGB1).[28,29] Increased production and recruitment of proinflammatory cytokines and chemokines have also been proposed to play a role in host response to ionizing radiation. These processes change the phenotype of tumor cells resulting in upregulation of cell-surface molecules that ultimately render these tumors more susceptible to T-cell-mediated anti-tumor effects.[30]

Additionally, local radiotherapy may have systemic effects. The abscopal effect has been described in patients treated with radiotherapy to select metastatic lesions leading to shrinkage of non-irradiated tumors outside of the radiation field.[31] Such "bystander" effects have been seen in murine models and in clinical studies of patients treated with immune therapy and radiotherapy with augmented T cell responses in both the primary and metastatic lesions both within and outside of the radiation field.[32,33] Radiotherapy is believed to emulate the effect of a vaccine by sensitizing the host immune system to recognize previously unnoticed tumor cells. High dose radiotherapy has been shown to improve antitumor T-cell responses and the upregulation of MHC molecules on cancer cells. However, as with PARPi, immunosuppressive pathways, such as PD-L1/PD-1 are also induced which inhibits the ability of radiotherapy to enhance a patient's immune system against the cancer cells. While upregulation of PD-L1 in the tumor microenvironment (TME) negatively impacts T-cell function and T-cell mediated anti-tumor activity, the combination of radiotherapy and anti-PD1 or anti-PDL1 blockade can potentiate the immune response of T-cells and intra-tumoral T-cell infiltration to enhance anti-tumor activity in these tumor cells. Therefore, the addition of a PD-L1 inhibitor to high dose radiation has the potential to mitigate the immunosuppressive effects of radiotherapy, thereby enhancing anti-tumor immune activity. Immune therapy may also modulate the tumor microenvironment by normalizing tumor vessels, enhance tumor vessel perfusion, thereby reducing tumor hypoxia and promoting radiosensitivity.[34,35]

A number of both preclinical studies and clinical trials in a variety of cancers have shown promising synergism between radiotherapy and immune therapy leading to enhanced treatment efficacy. The combination of radiotherapy and PD-L1 signaling blockade has been shown to improve not only local control, but also long-term survival compared with radiotherapy alone in mice models supporting the synergistic interaction between irradiation and anti-PD-L1 strategies.[32,33, 36, 37,38] Several Phase I and Phase II studies have tested both the safety and efficacy of radiation in combination with immune therapies in patients with a variety of cancers including TNBCs. Many have taken advantage of intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) to deliver high doses of focused radiation in a short period of time in order to elicit a heightened immune response.[39] Importantly, no increase in toxicity has been demonstrated when using SBRT with immune therapy agents (e.g. pembrolizumab) relative to either treatment alone in women with TNBC.[30,31,40] Indeed, in a recent Phase II trial, the combination of high dose radiotherapy to 1 to 4 lesions and pembrolizumab lead to a 33% overall response rate outside of the radiation field in heavily chemotherapy pre-treated mTNBC patients with acceptable rates of toxicity.[40] The combination of radiotherapy and immune therapy, therefore, appears to be more potent than either treatment alone.[32,33,41] There are several prospective trials utilizing concurrent radiotherapy with immune therapy particularly in lung cancer, melanoma, and head and neck malignancies and studies in oligometastatic breast cancer. Given the recent approval of atezolizumab plus nab-paclitaxel in mTNBC and no competing trials of PARPi, radiotherapy and immune therapy in mTNBC patients previously treated with chemotherapy and/or immune therapy, an opportunity arises to study the ability of radiation in combination with talazoparib and atezolizumab to elicit responses in heavily pretreated patients who are naïve to atezolizumab and/or restore sensitivity to atezolizumab in patients previously treated with this agent. Notably, this combination of treatments has not been studied in mTNBC PD-L1+ patients. The potential for concurrent talazoparib and high dose radiotherapy to enhance immune response to anti-PDL1 blockade is an

exciting opportunity for patients with mTNBC PD-L1+ tumors regardless of gBRCA status. Given the limited treatment options available for these patients and the potential to upregulate PD-L1 with talazoparib and radiotherapy, we will enroll gBRCA1/2 negative subjects with PD-L1 positive mTNBC to the proposed study.

### 1.5 Rationale for Radiation Dose and Timing

The optimal dose and timing of radiotherapy when given with PARPi or immune therapy in breast cancer patients is based on preclinical and small patient studies. Several preclinical and clinical studies indicate that PARPi given prior to and concurrently with radiotherapy enhances radiosensitivity of tumor cells.[16,42-49] Murine models of breast carcinoma indicate that repeated radiation doses of 8Gy x 3 fractions result in priming of CD8+T cells that mediate the abscopal effect in the context of immune checkpoint blockade, while higher doses of 12 Gy and above in a single fraction attenuates immunogenicity.[50] In vitro studies have also demonstrated that SBRT given over three daily doses of 10 Gy to breast cancer cell lines upregulates PD-L1.[39] From these studies, moderately hypofractionated doses of 8 Gy x 3 or 6 Gy x 5 appear to be more effective in priming the immune system for immune therapy compared to a single high dose XRT treatment.[51] Repeated fractions of 8 Gy have been shown to be effective at synergizing with CTLA-4 and PD-1 blockade.[50] In one case report of a PD-L1 inhibitor given concurrently with conventionally fractionated radiation, there was no increase in acute toxicities.[52] In studies of PD-1 inhibitors given with radiotherapy (30 Gy in 5 fractions) in mTNBC patients, four of 9 women assessed 13 weeks after radiation had stable or partial responses which were durable for at least 22 weeks, while side effects were mild and included fatigue, myalgia, and nausea.[40] The optimal timing of XRT with immune therapy has also been studied with CTLA-4 targeted therapy. In these preclinical and clinical studies, radiotherapy administered concurrently or immediately before CTLA-4 blockade was associated with the best abscopal responses.[51] Despite the excitement generated by the above studies, it is also important to acknowledge the results of the recent randomized, non-comparative phase 2 TONIC trial of primer treatments. In this study, mTNBC patients were treated with adriamycin, cyclosphosphamide, cisplatin, or 8Gy x 3 radiation to one metastatic lesion over a two-week period prior to nivolumab, a PD-1 inhibitor. Among all induction therapies, radiation produced a low ORR of 8% while doxorubicin produced a high ORR of 35%.[53] One potential reason for these disappointing results is the timing of the radiation. As noted above, previous studies indicate that PD-1 blockade must be initiated within a week of radiation completion and preferably concurrently to maximize synergy between radiotherapy and immune checkpoint blockade.[54] The timing of radiotherapy could explain the low ORR rates in the TONIC trial. Therefore, it is possible and likely that radiotherapy given to 1-4 lesions concurrently with talazoparib and immune therapy, as proposed in the current study, may improve upon the otherwise low response rates previously observed in mTNBC patients.

In this current study, we propose to initiate talazoparib 12 days before radiation (8Gy x 3 fractions administered every other day to 1 to 4 extracranial metastatic lesions to minimize the number of days of treatment while maximizing the potential for efficacy). Atezolizumab will be initiated after the first but prior to the second fraction of radiotherapy and preferably on the same day to elicit the highest potential response rates from the combination of these therapies.

### 1.6 Hypothesis

We hypothesize that talazoparib, high dose radiation, and atezolizumab will be effective, as measured by ORR, and safe in gBRCA negative mTNBC patients with PD-L1+ tumor infiltrate.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1 Objectives

#### 2.1.1 Primary Objective

Estimate objective response rate (ORR) of talazoparib, high dose radiotherapy and atezolizumab, eight weeks after the first dose of atezolizumab in non-irradiated lesion(s) of gBRCA1/2 pathogenic variant negative mTNBC patients whose tumors are immune cell (IC)-positive.

#### 2.1.2 Secondary Objectives

- Determine the frequency and severity of adverse events using CTCAE v 5.0 after induction talazoparib followed by concurrent talazoparib, high dose radiation, and atezolizumab given as second, third, or fourth-line treatment for PD-L1 positive metastatic triple negative breast cancer (mTNBC) (≥ 2 lesions)
- Obtain progression free survival (PFS) data in gBRCA 1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, radiation, and atezolizumab
- Obtain overall survival (OS) data in gBRCA 1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, radiation, and atezolizumab
- ORR by immune-related RECIST (irRECIST)
- Determine duration of overall response (DOR) to talazoparib, high dose radiation, and atezolizumab given in the second or third-line setting to gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate
- Determine disease control rate (DCR) in gBRCA1/2 negative patients with PD-L1 positive infiltrate treated with talazoparib, high dose radiation, and atezolizumab given in the second or third-line setting
- Determine time to progression (TTP) in gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, high dose radiation, and atezolizumab given in the second or third-line setting
- Determine adherence to prescribed talazoparib, high dose radiation, and atezolizumab in the second or third-line setting among PD-L1 positive mTNBC patients
- Determine best overall tumor response in each patient to talazoparib, high dose radiation, and atezolizumab in the second or third-line setting among PD-L1 positive mTNBC patients

#### 2.1.3 Correlative/Exploratory Objectives

- Assess patient reported outcomes (PRO) measures of quality of life and fatigue before talazoparib, during and after radiation and atezolizumab in mTNBC patients with PD-L1 positive infiltrate treated with talazoparib, radiation, and atezolizumab
- Collect and store peripheral blood and plasma collected from gBRCA1/2 negative mTNBC patients with PD-L1 positive infiltrate before, during, and after treatment with talazoparib, radiation, and atezolizumab. (Philanthropic institutional funds will be used to support such studies and additional funding sources will be identified to conduct future

studies that explore the relationship between ctDNA, inflammatory cytokines, and number and types of B cells and ORR, PFS, and OS as well as side effects of treatment including immune-related adverse events.)

- Collect and store FFPE of tumor tissue from any metastatic lesion and fresh tumor tissue from one non-irradiated metastatic breast cancer site before and after radiotherapy in a subset of patients from gBRCA1/2 negative mTNBC patients (n~10 patients) for future analyses. Of note, every effort should be made to biopsy the same non-irradiated site prior to and after radiotherapy. (Philanthropic institutional funds will be used to support such studies and additional funding sources will be identified to explore the relationship between the number and distribution of myeloid cells and ORR, PFS, and OS.

## 2.2 Endpoints

### 2.2.1 Primary Endpoint

The primary endpoint of the study is the objective response rate (ORR) in non-irradiated lesion(s) assessed 8 weeks after the first dose of atezolizumab in gBRCA 1/2 pathogenic variant negative mTNBC patients with PD-L1 positive infiltrate treated with induction talazoparib and then concurrent high dose radiotherapy and atezolizumab in the second or third line setting. This measure of response and timepoint were chosen to emulate the study design of Impassion130. Historic control data of ORR of 10% in gBRCA1/2 negative and 45% in gBRCA1/2 patients with mTNBC treated with PARPi and immune therapy in the 2nd or third line setting will be used.[11,25] The majority of patients enrolled on this study will be prescribed radiotherapy to palliate symptoms, prevent symptoms (e.g. bone fracture, neurological compromise, tumor invasion into critical structures), and prevent tumor growth in 1 to 4 metastatic lesions. Previous studies of PET/CT, MRI, CT of the chest, abdomen and pelvis as well as bone scan have been used to evaluate breast cancer metastases and response to immune therapy and radiotherapy.[7,55-58] In one study, 96% of patients had at least a partial response to radiotherapy on PET/CT with a median time to first post-therapy PET of 1.2 months (range; 0.5-4.1).[57] These imaging options are considered standard of care in patients and will be covered by insurance.

### 2.2.2 Secondary Endpoints

- Frequency and severity of adverse events using CTCAE v. 5.0 up to 12 weeks post first dose of atezolizumab will be described in patients treated with induction talazoparib followed by concurrent high dose radiation and atezolizumab given as second or third-line treatment for PD-L1 positive metastatic triple negative breast cancer (mTNBC) ($\geq$ 2 lesions)
- Progression free survival (PFS) is defined as the day of study treatment initiation until disease progression by RECIST 1.1 or death whichever occurs first.
- Overall survival (OS) is defined as the day of study treatment initiation until death from any cause.
- ORR by immune-related RECIST (irRECIST) which will include confirmed complete response (CR) + confirmed partial response (PR) determined as per irRECIST
- Duration of overall response (DOR) is defined as 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).

- Disease control rate (DCR) is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease.
- Time to progression (TTP) is defined as the day of study treatment initiation until disease progression by RECIST 1.1.
- Adherence to prescribed talazoparib, high dose radiation, and atezolizumab in the second or third-line setting among PD-L1 positive mTNBC patients measured by intravenous infusion, oral medication, and radiation treatment compliance with prescribed systemic therapy and radiation dose and days of treatment.
- Best overall tumor response is defined as the best response recorded from the start of the study treatment until disease progression/recurrence.

# 3. ELIGIBILITY CRITERIA

## 3.1 Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent and HIPPA for the trial.

2. Ages 18-75 years old at time of consent. Female or male patients allowed.

3. ECOG PS of 0-2, KPS $\geq$ 60%.

4. Biopsy proven metastatic triple negative breast cancer (estrogen receptor (</= 10%), progesterone receptor (</= 10%) and no overexpression of HER2 as evaluated by local institutions **with at least 2 exracranial lesions** of metastatic disease on imaging.

5. PD-L1 positive tumor infiltrate as defined as $\geq$1% on IHC using the SP142 Ventana Assay.

6. Known gBRCA1/2 status (gBRCA 1/2 negative [e.g. gBRCA wild-type, gBRCA variants of uncertain significance] are eligible]).

7. Patients must have at least 1 extracranial metastatic lesion of measurable or non-measurable disease by RECIST v1.1) that is amenable to high dose radiotherapy and at least one additional extracranial lesion of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) that will not be treated with radiotherapy on this study. Of note, lesions maybe in the same organ but must be 2 cm apart and breast lesions may be treated.

8. Patients must have received at least one and no more than three previous lines of systemic treatment in the advanced setting with or without immune therapy. Patients with disease recurrence or progression following neoadjuvant or adjuvant cytotoxic chemotherapy are not eligible unless they have received at least one line of chemotherapy with or without immune therapy in the advanced setting. **NOTE:** Targeted small molecules (e.g. tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies

that inhibit angiogenesis (e.g. bevacizumab, afilbercept) are not counted in the number of lines of therapy. Cytotoxic chemotherapy with or without immune therapy for advanced disease prior to protocol treatment is not permitted within 2 weeks of the protocol treatment. Patients may or may not have received radiotherapy or neoadjuvant or adjuvant chemotherapy in the treatment of their initial, non-metastatic breast cancer, but must be entered on study 2 weeks after their last dose of radiotherapy, last cycle of chemotherapy and biologic therapy (if applicable) for mTNBC and have sufficient resolution of side effects per physician assessment at time of talazoparib.

9. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 14 days prior to registration.
    - Absolute neutrophil count $\geq$ 1500/mcL
    - Platelets $\geq$ 100,000 mm
    - Anemia $\geq$ 9.0 g/dL (**NOTE:** The use of transfusion or other intervention to achieve Hgb $\geq$ 9.0g/dl is acceptable)
    - Serum creatinine $\leq$ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance $\geq$ 60 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5× institutional ULN
    - Total bilirubin $\leq$ 1.5× ULN OR direct bilirubin $\leq$ 1× ULN
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5× ULN unless liver metastases are present, in which case they must be $\leq$ 5×ULN
    - International normalized ratio (INR) or prothrombin time (PT) $\leq$1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
    - Activated partial thromboplastin time (aPTT) $\leq$ 1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

10. Patients must be eligible for radiotherapy, talazoparib, and atezolizumab.

11. Females of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to Cycle 1 Day 1. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

12. Women of childbearing potential and males must agree to use two effective methods of contraception or complete abstinence, from the time of signing the informed consent (females) or first day of study treatment (males), during the course of the study and for 7 months (females) and for 4 months (males) after the last dose of study drug.

13. Patients must not have active wound healing issues from surgery and sufficient resolution of surgical side effects, per physician assessment, at time of radiotherapy.

14. During participation on this study, no other investigation or commercial agents or therapy for cancer other than bisphosphonate, rank ligand inhibitors, atezolizumab, radiotherapy and talazoparib should be administered. **NOTE:** Patients may have received bisphosphonates or rank ligand inhibitors prior to and while on enrollment on study.

15. Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

### 3.2 Exclusion Criteria

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

1. gBRCA1/2 pathogenic variant positive

2. Four or more lines of cytotoxic chemotherapy for mTNBC.

3. Previous radiation to the metastases to be treated with radiation on this protocol.

4. Previous PARPi treatment (e.g. talazoparib, niraparib, olazaparib).

5. Progression of breast cancer within the first 3 months of prior immune therapy for non-metastatic or metastatic breast cancer.

6. Untreated CNS disease (patients with stable CNS disease for at least 28 days and asymptomatic treated CNS metastases are permitted).

7. History of leptomeningeal disease.

8. History of autoimmune disease that has required systemic treatment (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Use of systemic glucocorticoid or immunosuppressive medications at time of enrollment.

10. Severe, active co-morbidity such as CHF or unstable angina within last 6 months, transmural MI within the last 6 months.

11. Acute bacterial or fungal infection requiring IV antibiotics at time of registration.

12. COPD or other respiratory illness requiring hospitalization at time of registration.

13. HIV positive with CD4 count <200 cells/ microliter.

14. Current hormone replacement therapy use.

15. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy. Indolent cancers (such as low risk prostate or in-situ cancers) that are not being treated, are acceptable.

16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

18. Receipt of the last dose or treatment of anti-cancer chemotherapy, radiotherapy, surgery, endocrine therapy, targeted therapy, biologic therapy, or tumor embolization ≤ 2 weeks (4 weeks for any monoclonal Antibody (mAb), 6 weeks for nitrosoureas or mitomycin C) prior to first dose of study treatment, or has not recovered (i.e., to ≤Grade 1 or Baseline) from clinically significant adverse events (AEs) due to these previously administered agents.

## 4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. Subjects must be registered prior to starting protocol therapy.

## 5. TREATMENT PLAN

This is a Phase II study designed to assess efficacy and safety of talazoparib, high dose radiation, and atezolizumab in patients with metastatic TNBC that is PD-L1 positive. A total of 23 gBRCA pathogenic variant negative patients will be enrolled. All patients will be treated with induction talazoparib of 1mg PO daily starting Day 1. Patients will then receive 8 Gy x 3 fractions to 1-4 metastatic lesions beginning Day 12,13, or 14 and given QOD. 840 mg of atezolizumab will be given intravenously (IV) on Day 15 of the 1st cycle and then on Day 1 and Day 15 of the remaining cycles. The sequence of administration is not specified on the days in which talazoparib and atezolizumab are given on the same day. Each cycle equals 28 days. Treatment will continue until progression or severe toxicity.

A safety lead in of up to 6 patients will be performed. Immune-related and non-immune related adverse events will be tracked up to 12 weeks post initiation of atezolizumab, as the majority of treatment-related toxicities from talazoparib, radiation, and atezolizumab occur within this time period. Further details are described below.

## 5.1 Study Treatment Administration

| Drug[1] | Dose | Route | Schedule[2] | Cycle Length |
|---|---|---|---|---|
| Talazoparib | 1 mg | Orally | Day 1 to Day 28 | 4 weeks (28 days) |
| Atezolizumab | 840 mg | IV over 60 minutes | Day 15 of Cycle 1 then<br>Day 1 and Day 15 of subsequent Cycles | |
| Radiation | 8 Gy | NA | 3 fractions given QOD beginning<br>Day 12, 13 or 14 of Cycle 1 but<br>24-72 hours prior to 1st dose of Atezolizumab | |

[1] A window of ± 5 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs). Timing of Cycle 1 treatment should be followed as outlined.

### 5.1.1 Talazoparib

Talazoparib 1 mg total dose will be taken orally once a day on Day 1 through Day 28. Talazoparib can be taken with or without food. If a subject misses a dose, they should take their next dose at the scheduled time. The capsule should be swallowed whole and must not be dissolved or crushed. Subjects will be asked to complete a drug diary and bring the diary in addition to medication for reconciliation. For patients with moderate renal impairment (CrCl ≤ 59 mL/min) after Cycle 1, the recommended dose of Talazoparib is 0.75 mg once daily.

### 5.1.2 Atezolizumab

Atezolizumab 840 mg will be delivered as an IV infusion on Day 15 of Cycle 1 then Day 1 and 15 of each cycle starting at Cycle 2 (every 2 weeks). The initial dose will be delivered over 60 minutes (± 15). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes (+10 minutes/- 5 minutes). Atezolizumab infusions instructions outlined in the Table below.

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

#### 5.1.2.1 Guidelines for Medical Management of Infusion-Related Reactions (IRRs)

Guidelines for medical management of IRRs during the first treatment are provided in the Table below. For subsequent cycles, IRRs should be managed according to the package insert and institutional guidelines. Guidelines are provided below for reference.

### 5.1.2.2 Management Guidelines for Infusion-Related Reactions

| Event | Management |
|---|---|
| IRR, Grade 1 | ● Reduce infusion rate to half the rate being given at the time of event onset.<br>● After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.<br>● If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.<br>● Monitor vital signs as clinically indicated |
| IRR, Grade 2 | ● Interrupt atezolizumab infusion.<br>● Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen).<br>● After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.<br>● For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.<br>● Monitor vital signs as clinically indicated |
| IRR, Grade 3 or 4 | ● Stop infusion.<br>● Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen).<br>● Monitor vital signs as clinically indicated<br>● Hospitalization indicated for clinical sequelae (examples: renal impairment, pulmonary infiltrates)<br>● Permanently discontinue atezolizumab. [a] |

IRR = infusion-related reaction.

[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).

### 5.1.3 Radiation Therapy

The first dose of radiation to 1-4 extracranial metastatic lesions (breast treatment is allowed) will be given on Day 12, 13, or 14 of Cycle 1 and 24-72 hours prior to the first dose of atezolizumab (typically Day 15). If administration of XRT is outside this window, the site will contact HCRN who will contact the sponsor investigator for approval. Radiotherapy will continue for a total of 24 Gy to each targeted metastatic lesion at 8 Gy per fraction for a total of 3 fractions given every other business day excluding weekends and holidays. Delivering the first dose of atezolizumab just before but on the same day as the 2nd XRT fraction is preferable. Other radiation fractionation schemes are not allowed. Additional information is in Section 10.3.

PTV goal coverage is at least 95% of the PTV covered by at least 95% of the prescribed dose with dose not exceeding 115% of the prescribed dose. 1-4 metastatic target lesions separated by at least 2cm may be treated. Radiation treatment to previously irradiated lesions or within 2 cm of previously irradiated sites is not permitted.

**Variation acceptable** is 95% of the prescribed dose must cover $\geq$70% of the PTV (95% of the prescribed dose to 70-95% of the PTV is permitted.)

**Deviation unacceptable** is < 70% coverage of the PTV by 95% of the prescribed dose.

**Acceptable variation** for radiation treatment duration is radiation treatment completion of all three radiation fractions in >4 but ≤ 10 consecutive business days excluding holidays.

**Unacceptable Deviation** for radiation treatment duration is radiation treatment completion in > 10 consecutive business days excluding holidays.

Surgery is not allowed for 30 days prior to or during radiotherapy but may be permitted after radiotherapy is completed.

If re-irradiation of the index lesion (s) is deemed necessary after protocol treatment, it is preferred that re-irradiation be performed 3 months or later after initial radiation and after the last protocol assessment and should only be considered at least 4 weeks after initial treatment on protocol. If re-irradiation of the index lesion occurs, it must be documented.

## 5.2 Safety Lead In

Immune-related and non-immune related adverse events will be tracked up to 12 weeks post initiation of atezolizumab, as the majority of treatment-related toxicities from talazoparib, radiation, and atezolizumab occur within this time period. Accrual will be halted after the 3rd and 6th subject until the 12-week post atezolizumab timeframe is met.

The combination of talazoparib, radiation, and atezolizumab will be deemed **unsafe** if any of the following occur:

- Two of the first 3 patients enrolled develop Grade 2 irAEs and are unable to resume systemic therapy within 8 weeks due to treatment-related toxicities **OR**
- Two of the first 3 patients enrolled develop Grade 3 or higher irAEs **OR**
- Two of the first 3 patients enrolled develop:
    - Grade 3 or higher febrile neutropenia
    - Grade 3 thrombocytopenia with bleeding event
    - Grade 4 neutropenia, anemia, or thrombocytopenia
    - Any clinically meaningful Grade 3 non-hematologic event that leads to hospitalization or a medical intervention other than electrolyte or IVF support as deemed by site investigator
    - Any Grade 4 or higher non-hematological event with the exception of Grade 4 fatigue.

If these toxicities occur in 1 or fewer of the first 3 patients enrolled, the trial will proceed to enroll an additional three patients.

If 2 of the first 6 patients enrolled develop Grade 2 irAEs and are unable to resume systemic therapy within 8 weeks due to treatment-related toxicities or any of the above named Grade 3 or higher irAEs or non-irAEs, the study treatment will be deemed **unsafe** and the trial will be stopped.

If one or fewer of the first 6 patients enrolled develop one of the above toxicities, the trial will continue to enroll the remaining patients unless the treatment is found to be ineffective during the planned interim analysis or until enrollment is complete.

## 5.3 Concomitant Medications

Any concomitant medications and treatment will be recorded from 30 days prior to talazoparib and up to the Day 30 safety visit after study treatment is discontinued whether they are breast or non-breast cancer related therapies.

### 5.3.1 Allowed Concomitant Medications and Supportive Care

The following concurrent medications are permitted and should be recorded in the source documents and transferred to OnCore EDC:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures, such as antihistamines, and corticosteroids
- Bisphosphonates – patients may be on it already or may initiated treatment while on protocol therapy
- Agents used to assist in management of therapy-induced side effects (NSAIDS, gabapentin, venlafaxine)
- Diabetes management medication including metformin
- Rank Ligand inhibitors
- Pain medications
- P-gp inhibitors are allowed but talazoparib dose will be reduced to 0.75mg once daily when coadministered with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. When the P-gp inhibitor is discontinued, increase talazoparib dose after 3-5 half-lives oft eh P-gp inhibitor to the dose used prior to the intitiation of the P-gp inhibitor.

All supportive therapy will be given during the study period at the discretion of the treating physician(s) to optimize medical care as long as they are within the parameters of the protocol and documented on each site's source documents as concomitant medication:

- Anticonvulsants if indicated
- Anti-emetics may be given prior to each fraction to prevent nausea
- Antidiarrheal as indicated by symptomatic diarrhea
- Analgesic premedication or to avoid general discomfort during simulation and treatment is recommended when appropriate.
- Analgesic medications to decrease pain
- Medications for neuropathy (e.g. gabapentin)
- Corticosteroids if indicated
- Herbal products are at the treating physicians' discretion and should be captured on the concomitant medication forms.
- Nutritional supplementation may be administered per standard indications and should be captured on the concomitant medication forms.
- Highly active antiretroviral therapy (HAART) is permitted for HIV affected individuals
- Medications for gastritis and esophagitis including proton pump inhibitors and magic mouthwash
- G-CSF or pegylated G-CSF may be given in the rescue setting during protocol treatment and ANC must be recovered to entrance values for the protocol

### 5.3.2 Prohibited Concomitant Medications

- Anticancer therapies such as chemotherapy other than talazoparib, immunotherapies other than atezolizumab, targeted therapy other than radiotherapy, etc. other than allowed on protocol.
- Hormone replacement therapy (see exclusion criteria)
- Chronic immunosuppressive therapies

### 5.3.3 Medications not recommended

- Herbal medicine is not recommended during the treatment phase

## 5.4 Reproductive Information

Negative pregnancy test done ≤ 14 days prior to treatment, for women of childbearing potential only. Female subjects should be using highly effective contraceptive measures, and must have a negative pregnancy test or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
- Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, bilateral salpingectomy or tubal ligation

Women of childbearing potential and males must agree to use one highly effective method or two effective methods of contraception, from the time of signing the informed consent (females)/first day of study treatment (males), during the course of the study and for 7 months (females) and 4 months (males) after the last dose of study drug. Abstaining from heterosexual intercourse is considered an effective method of contraception.

### 5.4.1 Contraception Options

<table>
<tr><th>Highly effective methods</th><th>Other effective methods<br>(barrier methods)</th></tr>
<tr><td rowspan="2">Intra-uterine devices (IUD)</td><td>Latex condom</td></tr>
<tr><td>Diaphragm with spermicide; Cervical cap; Sponge</td></tr>
<tr><td colspan="2">If the highly effective method cannot be used, using two effective methods at the same time are recommended.</td></tr>
</table>

# 6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 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 Talazoparib Dose Modifications and Toxicity Management

Dose or treatment modification for talazoparib are allowable and may occur as dose reductions, interruptions (within a cycle), or dose delays (between cycles) during the cycle or at the start of a new cycle. Per package insert, the dose of the talazoparib may be reduced from 1.0 to 0.75 mg PO Daily. However, talazoparib should be withheld completely for the adverse reactions listed in the table below until blood levels resolve. Further dose reductions are allowed to 0.5 mg and 0.25mg PO daily per investigator's brochure. In general, cycles should be 28 days long unless the start of a new cycle is delayed. If doses are missed within a cycle and the AE resolves before the end of the cycle, then the patient can resume taking the talazoparib for the remainder of the cycle. The start of a new cycles should be delayed according to guidelines below if the AE requiring a dose hold has not resolved by Day 1 of the next planned cycle. Talazoparib should be withheld in the following scenarios:

| Adverse Reaction | Withhold Talazoparib until levels resolve to | Resume Talazoparib |
|---|---|---|
| Hemoglobin < 8g/dL | Hemoglobin > 9g/dL | Resume talazoparib at reduced dose |
| Platelet Count < 50,000/uL | Platelet Count ≥ 50,000/uL | |
| Neutrophil Count < 1,000/uL | Neutrophil Count ≥1,500/uL | |
| Non-hematologic Grade 3 or 4 | ≤ Grade 1 | Consider resuming talazoparib at reduced dose or discontinue |

For patients with moderate renal impairment (CrcL 30 – 59 mL/min), the recommended dose of Talazoparib is 0.75 mg once daily. For patients with severe renal impairment (15mL/min ≤crCL<30mL/min), the recommended dose of talazoparib is 0.5mg once daily. Talazoparib has not been studied in patients requiring hemodialysis.

Talazoparib dose will be reduced to 0.75mg once daily when coadministered with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil. When the P-gp inhibitor is discontinued, increase talazoparib dose after 3-5 half-lives of the P-gp inhibitor to the dose used prior to the initiation of the P-gp inhibitor.

Investigators should manage their patients according to medical judgment and specific dose delays or interruptions recommended by the talazoparib investigator's brochure (see Additional Information)

## 6.2 Atezolizumab Dose Modification and Toxicity Management

Treatment modification for atezolizumab is allowable and may occur as dose interruptions (within a cycle) or dose delays (between cycles). The dose of the atezolizumab should not be reduced. In general, cycles should be 28 days long unless the start of a new cycle is delayed. If doses are missed within a cycle and the AE resolves before the end of the cycle, then the patient can resume taking the atezolizumab for the remainder of the cycle but should still stop on Day 15 to maintain the 13-day break. The start of a new cycle should be delayed according to guidelines in Appendix I if the AE requiring a dose hold has not resolved by Day 1 of the next planned cycle.

Investigators should manage their patients according to medical judgment and specific dose delays or interruptions recommended by the atezolizumab investigator's brochure. See Appendix I for toxicity management guidelines. Atezolizumab is not withheld for hematologic adverse reactions.

## 6.3 Radiation Therapy Dose Modification and Toxicity Management

One to four extra-cranial metastatic lesions (breast treatment is allowed) will be each treated to a dose of 24 Gy at 8 Gy per fraction. The irradiated lesions may be measurable or non-measurable by RECIST v 1.1. criteria. The non-irradiated lesion must be measurable disease by RECIST v 1.1 criteria. Treatments should be given every other business day, excluding weekends and holidays. No dose reduction in radiation is permitted, but dose interruptions are allowed. Radiation treatment breaks for up to 3 consecutive business days (excluding planned holidays) for radiotherapy-related toxicities or personal reasons are allowed as per the investigator's best medical judgment.

## 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 outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression per RECIST 1.1 (**NOTE:** a follow-up scan 4 weeks after disease progression may be obtained at the discretion of the investigator to confirm disease progression if the clinician suspects pseudoprogression on imaging and feels the patient is deriving clinical benefit from the study treatment)
    - Local recurrence – defined as disease progression in sites treated with radiotherapy on this protocol. Radiologists will take care to differentiate treated, sclerotic reactions from true progression of disease.
    - Distant disease progression – defined as radiological evidence of disease progression or recurrence in location (s) other than those treated with radiotherapy on this protocol
- 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. **NOTE:** If 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 ≥ 64 days.

## 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<br>Cycle = 28 days | Screening | | On Treatment | | | | | | | | Safety follow up visit[9] | Long-term Follow up[10] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 | | | | Cycle 2 | | Cycle 3+ | | | |
| | -30 days | -14 days | Day 1 | Day 13 ± 1 day | Day 15 ± 2 days | Day 17 ± 3 days | Day 1 ± 5 days | Day 15 ± 5 days | Day 1 ± 5 days | Day 15 ± 5 days | 30 days post last dose + 7 days | Every 4 months (±30 days) |
| **REQUIRED ASSESSMENTS** | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | |
| Medical History[1] | X | | | | | | | | | | | |
| Physical Exam | | X | X | X | X | X | X | | X | | X | |
| Vital signs and ECOG Performance Status[2] | | X | X | X | X | X | X | X | X | X | X | |
| Patient Reported Outcomes[3] | | | X[3] | | | X | X[3] | | | X[3] | | |
| AEs & concomitant medications | | X | X | X | X | X | X | X | X | X | X | |
| **LABORATORY ASSESSMENTS** | | | | | | | | | | | | |
| Complete Blood Cell Count with diff (CBC)[4] | | X | X | X | X | X | X | X | X | X | X | |
| Comprehensive Metabolic Profile (CMP)[4] | | X | X | X | X | X | X | X | X | X | X | |
| Thyroid Function Testing[4] | | | | X[4] | | | | | X[4] | | | |
| Pregnancy test (serum or urine) (WOCBP)[4] | | X[4] | | | | | | | | | | |
| **DISEASE ASSESSMENT** | | | | | | | | | | | | |
| CT or MRI of chest, abdomen and pelvis[5] | X | | | | | | | | | X[5] | | X[5] |
| Bone Scan[5] | X | | | | | | | | | X[5] | | X[5] |
| PET Scan[5] | X | | | | | | | | | X[5] | | X[5] |
| **TREATMENT EXPOSURE** | | | | | | | | | | | | |
| Talazoparib[6] | | | Daily | | | | Daily | | Daily | | | |
| Radiotherapy[6] | | | | X[6] | X[6] | X[6] | | | | | | |
| Atezolizumab[6] | | | | | X[6] | | X | X | X | X | | |
| **SPECIMEN COLLECTION** | | | | | | | | | | | | |
| Archival Tumor Tissue[7] | X[7] | | | | | | | | | | | |
| Fresh Tumor Tissue[7] | | X[7] | | | | | X[7] | | | | | |
| Blood Samples[8] | | | X[8] | X[8] | X[8] | | X[8] | | | X[8] | | |
| **FOLLOW-UP** | | | | | | | | | | | | |
| Survival Status, Subsequent Therapy | | | | | | | | | | | | X |

CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

**Key to Footnotes**

1: Medical History; other data to be obtained during this assessment includes a trial awareness question. In addition, the following will be captured: self-reported race, gBRCA status, PD-L1 status based on the Ventana PD-L1 (SP142) assay, tumor mutation testing results if performed (such as FoundationOne or Guardant360), prior anti-cancer treatment including medications (chemotherapy, checkpoint inhibitors, etc) radiation (dose and sites treated) and/or surgery. Diagnosis and staging to include pathology report and TNM staging documentation. AJCC manual Ed 8 will be utilized. For subjects with known CNS metastases, a brain scan report showing stable CNS disease within 30 days prior to start of protocol is required.

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

3: Patient reported outcomes to include: Multidimensional Fatigue Inventory (MFI-20) and EORTC QLQ-30. Baseline assessments will be performed (1) prior to treatment Cycle 1 Day 1, (2) on the last day of radiotherapy (3) prior to Cycle 2 Day 1 (about 2 weeks after 1$^{st}$ dose of atezolizumab) (4) prior to treatment Cycle 3 Day 15 (about 8 weeks after the 1$^{st}$ dose of atezolizumab), and (5) prior to treatment Cycle 4 Day 15 (about 12 weeks after 1$^{st}$ dose of atezolizumab).

4: If screening (baseline) CBC and CMP were performed within 7 days of Cycle 1 Day 1 of treatment, these do not need to be repeated. Research blood samples for baseline specimen collection may be drawn up to 7 days prior to Cycle 1 Day 1. All laboratory assessments should be done prior to treatment. Thyroid Function testing should be performed just prior to first dose of atezolizumab and then every 2 cycles. TSH and T4 will be obtained. T3 including free versus total testing is at the discretion of the site investigator. For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required within 14 days prior to initiation of study treatment.

5: Tumor response assessment will consist of evaluation by CT or MRI scans of chest, abdomen and pelvis and a bone scan or whole body PET CT with/without MRI at screening then every odd numbered cycle starting Day 15 of Cycle 3 (8 weeks post first dose of atezolizumab and then about every 8 weeks). Imaging selected for each subject should remain the same throughout the study. If the site investigator suspects pseudoprogression on imaging and feels that the patient is deriving clinical benefit from study treatment, a follow-up scan 4 weeks later may be obtained at the discretion of the investigator. Tumor imaging to be done at D30 safety visit/treatment discontinuation is at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. MRI of the brain should be performed at screening only if suspected brain metastases or to evaluate known and treated brain metastases per standard of care. A window of ± 7 days may be applied to all radiology imaging. Both patient imaging and radiotherapy data from participating institutions will be exported from the institution's diagnostic imaging department and radiation treatment planning system in DICOM format, and subsequently anonymized using the Velocity Anonymize software from Varian Medical Systems, a software that anonymize images, contours, plan and dose data without compromising the essential links between these radiotherapy objects and thus preserving their ability to be imported in a different treatment planning system at another institution. This vendor-neutral data on patients analyzed in this proposal will be

collected on a dedicated research server already available at Emory. Research coordinators or assistants are able to submit standard of care imaging through the same method. (See Appendix III for detailed instructions).

6: See Section 5 for complete details regarding treatment administration. Each cycle = 28 days. Talazoparib will be given orally daily starting Cycle 1 Day 1. Subjects will receive a total of 3 fractions of radiation and the first dose of radiation therapy can be given on Day 12, Day 13 or Day 14. The first dose of atezolizumab will be given 24 to 72 hours after the first dose of radiation intravenously but prior to the 2$^{nd}$ dose of radiation and preferably same day. Atezolizumab will continue every 2 weeks (should align to Day 1 and Day 15 for subsequent cycles). For example, Talazoparib will start on Day 1 and continue daily. If radiation starts on Day 13, atezolizumab could be given on Day 15 just prior to the second dose of radiation also given Day 15. Then the last dose of radiation can be given on Day 17.

7: See Section 8 for details regarding correlative samples. If prior Ventana PD-L1 (SP142) Assay, results are not available, archival tissue should be sent for testing as this is considered standard of care. Archival tissue for research purposes will also be collected if available and stored for correlative analysis once funding is available. Archival tissue for correlative analysis should be requested at screening and shipped post-registration by C2D1. A biopsy may be performed from a metastatic lesion that will not be treated with radiation prior to talazoparib treatment on Cycle 1 Day 1 and again prior to treatment on Cycle 2 Day 1. Biopsy sample collections are optional and are limited to 10 subjects (total 20 biopsies) at the Emory site ONLY. Every attempt should be made to biopsy the same metastatic lesion in each consenting patient at each time point. If the baseline sample is not collected, a Cycle 2 sample should not be collected. Please see the Correlative Laboratory Manual (CLM) for details regarding collection, processing and shipping of these samples.

8: See Section 8 for complete details regarding correlative samples. Blood for correlative samples will be collected prior to treatment Cycle 1 Day 1 then prior to first dose of radiation (Cycle 1 Day 12, 13 or 14), prior to first dose of atezolizumab (around Cycle 1 Day 15), prior to Cycle 2 Day 1 (about 2 weeks after 1st dose of atezolizumab) and prior to Cycle 3 Day 15 (about 8 weeks after the 1st dose of atezolizumab). These samples are required. Please see the Correlative Laboratory Manual (CLM) for details regarding collection, processing and shipping of these samples.

9: Safety Follow Up: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of treatment. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be monitored by a member of the study team until the event is resolved, stabilized, determined to be irreversible by the site investigator or a new anti-cancer treatment starts, whichever occurs earlier.

10: Long Term Follow Up: For subjects who discontinue for reasons other than progressive disease, radiographic disease assessment should be performed per standard of care. This imaging may be done locally. Follow up will occur every 4 months up to 2 years after treatment discontinuation . Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. A window of ± 30 days will be applied.

# 8. BIOSPECIMEN STUDIES AND PATIENT REPORTED OUTCOME MEASURES

Please see the Correlative Laboratory Manual for details regarding collection, processing and shipping of the samples described below.

| Sample Type | Prior to Cycle 1 Day 1 | Prior to 1st dose of XRT Cycle 1 ~Day 13 | Prior to 1st dose of Atezolizumab Cycle 1 ~Day 15 | Prior to Cycle 2 Day 1 | Prior to Cycle 3 Day 15 |
|---|---|---|---|---|---|
| Plasma for circulating tumor DNA (ctDNA) | X | X | X | X | X |
| Plasma & Buffy Coat for Inflammatory Markers/Cytokines | X | X | X | X | X |
| Whole blood for B Cell Correlates & RNA | X | X | X | X | X |
| Archival Tissue | X | | | | |
| Optional Fresh Tumor Tissue for mass cytometry and RNA-seq* | X | | | X | |

Collection of longitudinal blood and tumor tissue samples will be stored to conduct future biomarker studies of response to talazoparib, high dose radiotherapy, and atezolizumab, disease progression both locally and systemically, as well as side effects of treatment including fatigue and hematologic and pulmonary toxicities. These samples will be stored until additional extramural funding is identified above pre-existing philanthropic institutional and investigator sources to support these correlative studies.

## 8.1 Tissue

### 8.1.1 Archival Tissue

If prior PD-L1 results are available and the testing was performed with the Ventana Assay, they are required. If prior results are not available, archival tissue should be sent for Ventana PD-L1 (SP142) Assay as this testing is considered standard of care.

Archival tissue for research purposes will also be collected and is required if available and patient consents to providing this tissue. SAMHD1 is recognized for its deoxynucleoside triphosphate (dNTP) triphosphohydrolase activity, which restricts HIV-1 and other viral infections, and for mutations associated with Aicardi Goutières syndrome (AGS), an autoimmune disorder. SAMHD1 is also dysregulated in human cancers, including overexpression in 27% of breast cancers. Importantly SAMHD1 deficiency in breast cancer cells caused PARPi hypersensitivity, suggesting that SAMHD1 levels may function as a biomarker for response to PARPi. Our plan is to use philanthropic institutional and investigator funds and seek extramural funding to perform immunohistochemistry (IHC) on preoperative breast cancer tumor samples from this study to determine the significance of SAMHD1 levels

on predicting response to PARPi, radiation, and atezolizumab. We have anti-SAMHD1 antibodies that specifically recognize SAMHD1 in breast cancer tumor samples by IHC.

### 8.1.2 Fresh Tissue

Optional fresh tissue will be collected prior to starting treatment Cycle 1 Day 1 and prior to treatment Cycle 2 Day 1. A sample from the same non-irradiated site should be collected at both time points. A maximum of 10 paired samples will be collected from the Emory site ONLY. If the baseline sample is not collected, a Cycle 2 sample should not be collected.

## 8.2 Peripheral Blood Samples

Blood for correlative samples will be collected prior to treatment Cycle 1 Day 1 then prior to first dose of radiation, first dose of atezolizumab, Cycle 2 Day 1 (about 2 weeks after 1st dose of atezolizumab), and Cycle 3 Day 15 (about 8 weeks after the 1st dose of atezolizumab). These samples are required.

### 8.2.1 Circulating Tumor DNA

Plasma levels of ctDNA identified by tp53 mutations, brca1 and/or med12 are found in up to 88% of TNBC tumors.[3,4] ctDNA will be measured using targeted assays to detect point mutations in tp53, brca1 and/or med12 that may provide insight into response or lack of response to proposed therapy. Plasma can be frozen for future ctDNA extraction, an advantage for this study given the number of proposed enrollment centers and the fact that we will use pre-existing philanthropic, institutional funds and seek additional funding to support these investigations.

### 8.2.2 B Cell Correlates and RNA

In previous work published by Dr. Kavita Dhodapkar (co-investigator on future study of translational endpoints), her group demonstrated changes in the number and types of B cells following once cycle of combination checkpoint blockade with either anti-CTLA4 and/or anti-PD1 immune therapy in melanoma patients.[5] An early decline in the number of circulating B cells correlated with both the timing and severity of immune-related adverse events (irAES). Immune therapy led to changes in circulating B cells shortly after initiation of treatment, including a decline in circulating B cells and an increase in $CD21^{l}$ B cells and plasma blasts. There was also greater clonality with B cell receptor sequencing and a higher frequency of clones compared with CD21 high cells. At least a 70% decline in circulating B cells and a 2-fold increase in circulating $CD21^{lo}$ B cells and plasma blasts following combined checkpoint blockade associated with irAEs, and these changes in B cell distribution preceded irAEs by a median of 3 weeks (0-10 weeks). Treatment-induced changes in b cells were correlated with both the frequency and timing of irAEs such that patients with early B cell changes experienced higher rates of grade 3 or higher irAEs 6 months after immune checkpoint blockade.[5] Based on this preliminary data, early changes in B cells may help identify patients at increased risk of irAEs. This data supports the exploration of B cell changes in response to the combination of talazoparib, radiotherapy and immune therapy and to examine whether Bcell changes predict treatment-related irAEs.

### 8.2.3 Inflammatory Markers/Cytokines

Plasma concentrations of sTNFR2 and IL-6 will be determined as previously described using sandwich ELISA according to manufacturer's protocol (R & D Systems, Minneapolis, MN).

High sensitivity CRP will be measured using a standard turbidimetric assay. These inflammatory markers have been associated with of depression and fatigue in our previous studies of breast cancer patients [6-8], as well as other studies of pain in breast cancer patients.[9,10] These samples will be shipped to Dr. Andrew Miller's laboratory at Emory University. Philanthropic institutional funding is secured to run biomarkers studies of symptoms related to treatment, concentrations of sTNFR2, IL-1ra, and IL-6 will be determined using sandwich ELISA according to manufacturer's protocol (R & D Systems, Minneapolis, MN). We will also seek additional extramural funding to support this research. Each determination (excluding the soluble cytokine receptors which require less sample) requires 100-150 ul of sample; all samples will be assayed in duplicate. Quality control plasma of both low and high cytokine concentrations will be included with every assay. The mean inter- and intra-assay coefficients of variation for control samples are reliably 10% or less. Dr. Miller is a Professor in the Emory Department of Psychiatry and Behavioral Sciences and has extensive experience conducting these assays and performing studies on the impact of inflammation on the brain and behavior in cancer patients. CRP will be measured in the CLIA certified laboratory of the Emory University Hospital using a standard turbidimetric assay. RNA will also be collected from PBMCs to explore biomarkers of outcome.

### 8.3 Genetic Testing

Participants will be given information as part of the informed consent process that samples will be used for research purposes that will include genetic testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case where an incidental genetic finding is identified, the sponsor investigator of this project will be notified. Possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of Emory University and local/participating site IRBs, as applicable, will be followed. Any additional approvals that may be required prior to participant notification will be secured in advance.

### 8.4 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples after study-specific correlative research has been completed. Hoosier Cancer Research Network (HCRN) will manage the banked samples. Samples will be coded and banked indefinitely in the Hoosier Cancer Research Network Biorepository.

### 8.5 Confidentiality of Biospecimens

Samples will be identified by the subject's study number 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 study number.

### 8.6 Patient Reported Outcome Measures

Completion of Patient Reported Outcomes instruments is critical for understanding the impact of talazoparib, high dose radiotherapy, and atezolizumab given for metastases in TNBC patients.

Quality of life (EORTC QLQ-C30) and fatigue (MFI-20) will be evaluated as secondary endpoints. The bodily domain of the EORTC QLQ-C30 will allow for assessment of patients who present for symptoms other than pain.[59]

Both instruments are of minimal burden to patients and take approximately 20 minutes to complete. At Emory, ongoing longitudinal studies of patients receiving radiotherapy in the definitive and metastatic setting have used an overlapping set of instruments and established feasibility with over 95% compliance with completing these forms.

### 8.6.1 European Organization for Research and Treatment Quality of Life Questionnaire Core-C30 (EORTC QLQ-C30)

EORTC QLQ-C30 is one of the most widely used general health-related quality of life questionnaires in oncology for patients with metastatic disease and palliative care research. This 30-item questionnaire contains items/scales pertaining to pain, physical function, emotional function, fatigue, global health status/quality of life, nausea/vomiting, appetite, dyspnea, constipation and sleep.[60] The instrument has been validated in multiple cancer patient populations with metastatic disease and has been used in trials of mTNBC patients including IMpassion130.[7,61]

### 8.6.2 Multidimensional Fatigue Inventory (MFI-20)

MFI-20 will be used to evaluate the presence and severity of fatigue among subjects by self-report.[62] The MFI-20 assesses 5 dimensions of fatigue, including general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation.[63,64] The MFI has been used to quantify fatigue in cancer patients, and a minimal clinically important difference of 10 points has been established.[65] Fatigue is one of the more common patient reported symptoms from PARPi and immune therapies and may severely impact QOL. Therefore, a separate instrument specifically devoted to accurately measuring this important symptom will be employed.

## 9. CRITERIA FOR DISEASE EVALUATION

All subjects should be assessed for response using both RECIST 1.1 and irRECIST criteria at each timepoint. Once a subject progresses per RECIST 1.1, disease evaluation per irRECIST will continue and RECIST 1.1 response is no longer required.

### 9.1 Evaluation using RECIST 1.1

### 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. 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 non-irradiated 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 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)<br><br>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.

In some circumstances, investigators may suspect pseudoprogression but the clinician feels the patient is deriving clinical benefit from study treatment. A follow-up scan 4 weeks later may be obtained at the discretion of the investigator in these cases to evaluate disease status.

## 9.2 Immune-Related RECIST (irRECIST)

### 9.2.1 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.

### 9.2.2 Non-measurable Lesion Definitions
Follow definitions from RECIST 1.1.

### 9.2.3 Non-target lesions will include
- Measurable lesions not selected as target lesions
- All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest perpendicular diameter is ≥10 and < 15 mm.
- Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.

### 9.2.4 Target and Non-Target Lymph Node Lesion Definitions
Follow definitions from RECIST 1.1

### 9.2.5 Non-Target Lesion Selection
All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

### 9.2.6 Bone Lesions
Follow 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.

### 9.2.7 Cystic and Necrotic Lesions as Target Lesions
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.

### 9.2.8 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.

### 9.2.9 Baseline

- The longest diameters of non-nodal target and short axes of nodal target measurable lesions will be recorded. Together they determine the Baseline Total Measured Tumor Burden (TMTB).

### 9.2.10 Follow-up

- 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

### 9.2.11 Evaluation of Best Overall Response per irRECIST

| % Change in Sum of the Diameters | Target Lesion Definition | Non-Target Lesion Definition | New Measurable Lesions | New Unmeasurable Lesions | Overall Immune Related RECIST Timepoint Response |
|---|---|---|---|---|---|
| 100% decrease from baseline[a] | CR | CR | No | No | CR |
| 100% decrease from baseline[a] | CR | Non-CR or not all evaluated | No | No | PR |

| | | | | | |
|---|---|---|---|---|---|
| ≥ 30% decrease to <100% decrease from baseline | PR | Any | Yes or no | Yes or no | PR |
| < 30% decrease from baseline to < 20% increase from nadir | SD | Any | Yes or no | Yes or no | SD |
| Not all evaluated | Not evaluated | Any | Yes or no | Yes or no | NE |
| ≥ 20% increase from nadir | PD | Any | Yes or no | Yes or no | PD |
| CR =complete response; NE= not evaluable; PD=progressive disease; PR =partial response; RECIST =Response Evaluation Criteria in Solid Tumors; SD= stable disease. | | | | | |
| [a] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR. | | | | | |

# 10 DRUG AND RADIATION INFORMATION

## 10.1 Talazoparib

See the investigator's brochure for complete details regarding this medication.

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2, which play a role in DNA repair. In vitro studies with cancer cell lines that harbored defects in DNA repair genes, including BRCA 1 and 2, have shown that talazoparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, decreased cell proliferation, and apoptosis. Talazoparib anti-tumor activity was observed in human patient-derived xenograft breast cancer tumor models that expressed mutated or wild-type BRCA 1 and 2.

### 10.1.1 Supplier/How Supplied

Talazoparib capsules are supplied by Pfizer, Inc at no charge to subjects participating in this clinical trial as described in Section 5.

The drug product is a capsule formulation composed of a blend of talazoparib tosylate drug substance and silicified microcrystalline cellulose filled into a hypromellose capsule. The capsules are presented in strengths of 0.10 mg, 0.25 mg, and 1.0 mg (free base equivalent), distinguished by capsule color and described in milligrams per capsule. Capsules are provided in high-density polyethylene (HDPE) bottles, with induction-sealed closures, containing 30 drug product capsules of a single strength.

The investigator and each participating site 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 Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

### 10.1.3 Adverse Events
See the current investigator's brochure for complete details regarding adverse events related to this medication. Most common adverse reactions (≥10%) were alopecia, diarrhea, dizziness, dysguesia, dyspepsia, fatigue, headache, hyperglycemia, increase liver function tests, hypocalcemia, loss of appetite, myelosuppression, nausea, vomiting, abdominal pain, and hyperbilirubinemia. Please see package insert for a detailed list of side effects. Cases of MDS and AML have been reported in patients treated with talazoparib.

## 10.2 Atezolizumab
See the investigator's brochure for complete details regarding this medication.

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.

### 10.2.1 Supplier/How Supplied
Genentech will supply atezolizumab at no charge to subjects participating in this clinical trial as described in Section 5.

Atezolizumab Injection, 840/14 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, 14-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 14 mL (840 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 14 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.

The investigator and each participating site 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.

### 10.2.2 Preparation
*Atezolizumab Injection, 840 mg/14 mL (60 mg/mL)*
Atezolizumab in Formulation F05 (840 mg per vial) will be administered in 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 or 0.22 μm in-line filters. Atezolizumab

should only be diluted with 0.9% sodium chloride injection USP. 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 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 to concentrations between 3.2 mg/mL and 16.8 mg/mL 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.

### 10.2.3 Storage and Stability

*Atezolizumab Injection, 840 mg/14 mL (60 mg/mL)*
Atezolizumab (F05) and the diluent must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt for up to 24 hours or at ambient temperature ≤ 25°C (77°F) for 8 hours. This time includes storage and time for administration for infusion. If the dose solution is stored at 2°C−8°C (36°F−46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. Do not shake or freeze infusion bags containing the dose solution.

This time 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.

### 10.2.4 Adverse Events

See the current investigator's brochure for complete details regarding adverse events related to this medication.

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.

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).

## 10.3 Radiotherapy

The Radiotherapy Treatment Phase is the time period between and including the first and last day of radiotherapy. Enrolled patients will be treated with induction talazoparib (C1D1). The first dose of radiation will be given on Days 12, 13, 14 of the first cycle of talazoparib. Patients will be treated with atezolizumab (C1D15) 24-72 hours after the first dose radiotherapy and prior to and preferably on the same day as the 2$^{nd}$ dose of radiotherapy. High dose radiotherapy will

be given to as many as 1-4 extracranial metastatic lesions (measurable or non-measurable by RECIST v 1.1 criteria) 24-72 hours prior to the first dose atezolizumab (i.e. Day 13, 14, 15, 16 or 17 of Cycle 1) and every other day (e.g. XRT Fraction 2 - Day 14, 15, or 16 and XRT Fraction 3 - Day 16, 17, or 18) for a total of 3 fractions (8 Gy each).

Patients will undergo CT simulation in preparation for radiation planning. 4-dimensional CT will be used for tumors in the lungs or liver at the discretion of the treating physician. Axial CT images will be obtained throughout the target lesion(s). The gross tumor volume (GTV) will be defined as the visible tumor on CT and/or MRI imaging +/- PET or if 4DCT is used, an internal target volume (ITV) will be defined using all phases of the 4DCT simulation and the diagnostic CT and/or MRI and/or PET/CT as reference. No additional margin will be added for microscopic spread of disease. Clinical target volume will equal GTV or ITV based on CT or 4DCT simulation images and provider discretion . A planning target volume (PTV) margin of 2-5mm will be added to the GTV or ITV depending on site of disease, immobilization, and institutional set-up accuracy: 2mm for spinal treatments and 5mm for other sites are generally recommended. For vertebral lesions, the entire vertebral body may be considered the GTV/CTV, as per institutional practice.

Patients can be treated with 3-D, intensity modulated radiation therapy (IMRT), SBRT, and/or Volumetric Arc Therapy (VMAT). 6-20 MV photon beams or proton treatment is allowed. Cobalt-60 and electron treatment is not allowed.

1-4 extracranial metastatic target lesions separated by at least 2cm may be treated on protocol. Radiation treatment to previously irradiated sites or within 2cm of previously irradiated sites is not permitted.

### 10.3.1 Dose Fractionation

24 Gy at 8 Gy per fraction given every other business day excluding weekends and holidays are allowed on this protocol. Other radiation fractionation schemes are not allowed.

95% of the prescribed dose must cover $\geq$95% of the PTV (95% of the prescribed dose to 70-95% of the PTV is permitted and is considered Variation Acceptable). Deviation unacceptable is < 70% coverage of the PTV. Dmax should not exceed $\geq$ 115% and is not permitted on this study. These criteria should be evaluated for each metastasis independently not including dose in the treatment of all other metastases. Unacceptable Deviation is treatment completion in >10 consecutive business days excluding holidays.

All institutions must use heterogeneity correction dose calculation algorithms.

### 10.3.2 Isocenter Placement

It is best to place isocenter near the center of the target lesion. If there are multiple lesions that cannot be treated in a single field, multiple isocenters should be placed with each centered in a separate target lesion.

### 10.3.3 Patient Immobilization, Simulation, and Localization

Participating subjects will be positioned in a reproducible, comfortable, and stable pose to allow for both reliable and accurate target position during treatment. The immobilization and pose must be reliable enough to ensure that the GTV does not deviate beyond the confines of the PTV. Ideally, multiple metastases treated on this study would be treated in one treatment position. However, more treatment positions can be used at the discretion of the treating radiation oncologist.

CT-based treatment planning and image guided radiotherapy (IGRT) is required for all patients. The CT scan must encompass the target metastases, as well as the following necessary organs at risk (OAR) when included in the radiation field:

- Heart
- Organ
- Lungs
- Liver
- Kidneys
- Spinal Cord
- Brain
- Brainstem
- Lens
- Bowel Bag
- Brachial plexus

CT scans should have uniform slice thickness of $\leq$5mm. The use of IV contrast is left to the discretion of the treating radiation oncologist but is not required.

On board imaging (OBI) using KV, MV x-rays, cone beam CT or CT every fraction is required. (IGRT is required).

### 10.3.4 Target Volumes

The treating radiation oncologist will contour the gross tumor volume (GTV) and planning target volume (PTV), as well as relevant normal structures within 2cm of the radiation field (e.g. spinal cord, kidneys, lung, bowel bag, and heart).

### 10.3.5 Planning priorities for Organs at Risk

An unacceptable deviation will be assigned to radiation plans which exceed the absolute limits of the spinal cord, cauda equina, sacral plexus, or brachial plexus (See below).

Every effort will be made to cover 100% of the PTV with 100% of the prescribed dose. Ultimately, at least 95% of the PTV must be covered by at least 70% of the prescribed dose or the plan will be considered deviation unacceptable. Radiation plans will be considered unacceptable if any of the criteria below in the table "**CRITICAL ORGAN DOSES**" are **not** fulfilled.

**CRITICAL ORGAN DOSES**

| Structure | Volume | Dose/Volume |
|---|---|---|
| Spinal Cord | <0.03cc | 21.9 Gy |
| | <1.2cc | 13 Gy |
| Brachial plexus | <0.03cc | 24 Gy |
| | <3 cc | 22 Gy |
| Cauda equina | <0.03cc | 24 Gy |
| | <5 cc | 21.9 Gy |
| Sacral plexus | <0.03cc | 24 Gy |
| | <5 cc | 22.5 Gy |
| Trachea and Ipsilateral Bronchus | <0.03 cc | 30 Gy |
| | <5cc | 25.8 Gy |
| Small Bowel | <0.03cc | 25.2 Gy |
| Large Bowel | <0.03cc | 28.2 Gy |
| Total Lungs | V20 | <15% |
| | V11 | <37% |
| | V10.5 | <1500 cc |
| | V11.4 | <1000 cc |
| Esophagus | <0.03cc | 25.2 Gy |
| | <5 cc | 17.7Gy |
| Kidney, bilateral | V15 | <200cc |
| Kidney, bilateral | V12 | <55% |
| Heart | Mean | <20 Gy |
| | <0.03cc | 30 Gy |
| | <15 cc | 24 Gy |
| Brain, brainstem | <0.03cc | 23.1 Gy |
| Liver (Normal liver-gross tumor volume if within liver) | ≥700cc | <15Gy |
| Duodenum | $D_{1cm^3}$ | <30 Gy |
| | <0.03 cc | 22.2 Gy |
| | <10 cc | 15 Gy |
| Small bowel | $D_{2cm^3}$ | <21 Gy |
| Small bowel | $D_{5cm^3}$ | <30 Gy |
| Large bowel | <0.03 cc | 34.5 Gy |
| | <3.5cc | 24 Gy |
| Rectum | <0.03cc | 28.2 Gy |
| | <20 cc | 24.0 Gy |
| Bladder | 0.03 cc | 28.2 Gy |
| | <15 cc | 16.8 Gy |
| Ureter | <0.03cc | 40 Gy |
| Penile Bulb | <3cc | 25 Gy |
| Great vessels | <0.03cc | 45 Gy |
| | <10 cc | 39 Gy |
| Skin | <0.03cc | 33 Gy |

| | | |
|---|---|---|
| | <10cc | 31 Gy |
| Stomach | <0.03cc | 22.2 Gy |
| Femoral heads | <10 cc | 21.9 Gy |
| Bile duct | <0.03 cc | 36 Gy |
| Renal hilum/vascular trunk | <15 cc | 19.5 Gy |
| Rib | <0.03 cc | 36.9 Gy |
| | <5cc | 40 Gy |

### 10.3.6 Composite Dose Calculations

When more than one radiation field is used to treat multiple metastases, composite plans which include total dose summation from the multiple treatment sites on a single CT scan that encompasses relevant anatomy, must be generated to incorporate dose to surrounding normal tissues. These composite plans must include a planning CT dataset that incorporates all targets and relevant critical structures. When more than one field is used to treat multiple metastases, it is advisable to treat all lesions with the patient in the same position. Contact HCRN who will contact the sponsor-investigator, Dr. Mylin Torres, if there are technical challenges in summing dose and generating composite plans.

Composite dose plans including all treated metastases and OARs must be submitted. To facilitate composite planning, dose to all metastases should be calculated on a single CT scan. If this is not possible, dose from each separate metastasis treatment plan should be generated and incorporated on the composite plan.

### 10.3.7 Documentation Requirements

Treatment interruptions, including reasons for treatment breaks, must be clearly documented in the treatment record. However, treatment interruptions should be avoided generally.

Sites will record radiation dose-volume values for all required structures on a datasheet which will be submitted with the digital radiation data to Emory University for review.

If re-irradiation of the index lesion is deemed necessary after protocol treatment, it is preferred that re-irradiation be performed 3 months or later after initial radiation and after the last protocol assessment and should only be considered at least 4 weeks after initial treatment on protocol. If re-irradiation of the index lesion occurs, it must be documented.

# 11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. A copy of the CTCAE v5 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the EDC system (Documents and Information Tab).

## 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 Hepatocellular Carcinoma that were not present prior to the AE reporting period.
- Preexisting medical conditions - A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- Diagnosis vs. Signs and Symptoms: **NOTE:** If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

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. All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death". **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.
- If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
    - Hospitalizations for the following reasons do not require reporting:
    - Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
    - Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
    - Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study
- 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 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.

### 11.1.3 Adverse Events of Special Interest (AESI)

The following AEs are considered of special interest:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:

  - Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 × ULN (or > 3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

#### 11.1.3.1 Atezolizumab AESIs

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- 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)

### 11.1.4 Expected/Unexpected Adverse Event

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

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.

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

### 11.1.5 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) |

### 11.1.6 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (V5 .0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated d |
| 5 | Death related to adverse event [d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (V5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

## 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.

### 11.2.2 Serious Adverse Events (SAEs)

#### 11.2.2.1 Site Requirements for Reporting SAEs or irAEs to HCRN

- SAEs will be reported 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.
- SAEs include events related and unrelated to the study drug(s).
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form will 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 above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

### 11.2.3 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior Atezolizumab and talazoparib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period.

## 11.3 Special Situation Reports

### 11.3.1 Pregnancy reports

If a female subject or female partner of a male study subject becomes pregnant while receiving the study drug or within 7 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE to HCRN **within thirty (30) calendar days of the awareness date**. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

### 11.3.2 Other Special Situation Reports

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to HCRN **within thirty (30) calendar days**.

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

### 11.3.3 Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to HCRN **within fifteen (15) calendar days** of the awareness date. A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

## 11.4 HCRN Requirements for Reporting SAEs to Genentech

HCRN will report all protocol-defined Adverse Events (AEs)/SAEs, AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product to Genentech **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Genentech as it is received from site.

Genentech Drug Safety at:
Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:
**Email: kaiseraugst.global_impcomplaint_management@roche.com**

### 11.5 HCRN Requirements for Reporting SAEs to Pfizer

HCRN will report all SAEs to Pfizer within 1 business day of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Pfizer as it is received from site. Pfizer Drug Safety: Via fax: Pfizer U.S. Clinical Trial Department 1-866-997-8322 or email: USA.AEReporting@pfizer.com

### 11.6 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. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

### 11.7 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. All written IND Safety Reports submitted to the FDA by HCRN on behalf of the sponsor-investigator must also be faxed to Genentech 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. A copy of these documents will be available to Genentech upon request.

### 11.8 IND Safety Reports Unrelated to this Trial

Genentech will provide to HCRN 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

### 12.1 Study Design

This is a Phase II unblinded single arm study designed to determine the efficacy and safety of talazoparib, high dose radiation, and atezolizumab given as second or third-line treatment to gBRCA pathogenic variant negative mTNBC (≥ 2 lesions) patients with PD-L1 positive tumors who have progressed on one to three lines of prior chemotherapy with or without immune therapy.

## 12.2 Sample Size and Accrual

Sample size is determined using Simon's 2-stage Minimax design to detect a 20% increase in objective response rate (ORR). The null hypothesis that the true response rate among gBRCA1/2 negative patients of 10%, based on the TOPACIO study[25], will be tested against a one-sided alternative. In the first stage, 7 patients will be accrued. If there are 0 responses in these 7 gBRCA1/2 negative patients, the study will be stopped. Otherwise, 11 additional patients will be accrued for a total of 18 evaluable patients. This design yields a Type I error rate of 0.1 for one sided test and power of 80% when the true response rate is 30% in the gBRCA pathogenic variant negative patients. Assuming an attrition rate of 20%, we will enroll 23 total gBRCA 1/2 negative patients.

## 12.3 Endpoints

### 12.3.1 Definition of Primary Endpoint

The objective response rate is the proportion of all subjects with confirmed PR or CR in non-irradiated lesions according to RECIST v.1.1. Response will be assessed by the Investigator 8 weeks after the first dose of atezolizumab as was previously done on the Impassion130 Trial.[7]

### 12.3.2 Definition of Secondary Endpoints

- Frequency and severity of adverse events scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 up to 12 weeks post 1st dose of atezolizumab will be described. The adverse events will be summarized descriptively using frequencies and percentages of all captured toxicities and grades using CTCAE v.5 criteria. We will determine whether talazoparib and targeted, high dose radiotherapy to 1-4 lesions in combination with atezolizumab in mTNBC patients (≥ 2 lesions) adversely increases the frequency and severity of toxicities associated with any of these agents alone when given in isolation, including Grade 2 or higher irAEs, hematologic toxicities, pneumonia, pneumonitis and fatigue.
- Progression Free Survival is a measurement from Cycle 1 Day 1 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.
- Overall Survival is defined by the date of Cycle 1 Day 1 to date of death from any cause.
- ORR by immune-related RECIST (irRECIST) which will include confirmed complete response (CR) + confirmed partial response (PR) determined as per irRECIST
- Duration of Overall Response is 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).
- Disease Control Rate is the proportion of all subjects with stable disease (SD), or partial response (PR), or complete response (CR) according to RECIST 1.1, for 8 weeks from the start of talazoparib until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).
- Time to Progression is measurement from the date of Cycle 1 Day 1 until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease

evaluation or date of death.

- Adherence, measured by intravenous infusion, oral medication, and radiation treatment compliance with prescribed systemic therapy and radiation dose and days of treatment.
- Patient-reported outcomes (PROs) include 1) Fatigue, as measured by MFI, actual scores and change from baseline; 2) Health Related Quality of Life, as measured by EORTC QLQ-C30, actual scores and change from baseline.
- Best overall tumor response is defined as the best response recorded from the start of the study treatment until disease progression/recurrence.

## 12.4 Assessment of Safety

All patients who receive at least one dose of talazoparib will be evaluable for toxicity. The adverse events will be summarized descriptively using frequencies and percentages of all captured toxicities and grades using CTCAE v.5 criteria. We will determine whether talazoparib and targeted, high dose radiotherapy to 1-4 lesions in combination with atezolizumab in mTNBC (≥ 2 lesions) patients adversely increases the frequency and severity of toxicities associated with any of these agents alone when given in isolation, including Grade 2 or higher irAEs, hematologic toxicities, pneumonia, pneumonitis and fatigue. Please refer to the Study Calendar for the schedule of toxicity assessments.

## 12.5 Assessment of Efficacy

All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of response. The ORR is the primary assessment of response and is the proportion of all subjects with confirmed PR or CR in non-irradiated sites according to RECIST 1.1 and will be assessed 8 weeks after the first dose of atezolizumab. ORR by irRECIST will also be measured. We will perform this analysis with and without patients who received at least one cycle of treatment and have their disease re-evaluated. In addition, progression free survival, as well as duration of overall response, disease control rate, and time to progression will be measured according to RECIST 1.1 and irRECIST. Overall survival will also be measured.

## 12.6 Data Analysis Plans

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided 95% confidence intervals (CIs) will be provided where appropriate. Time-to-event analyses will be performed using Kaplan-Meier methods. Any statistical analysis to be performed among subgroups is for descriptive and future study purposes.

### 12.6.1 Analysis Plans for Primary Objective

Overall response rate (ORR) in non-irradiated lesions 8 weeks post-atezolizumab. ORR rate is defined as the number of patients who develop a partial response (PR) or complete response (CR) divided by the total number of patients. The ORR will be estimated, and a 95 % confidence interval will be reported using Wilson interval (Wallis, SA. Binomial confidence intervals and contingency tests: mathematical fundamentals and the evaluation of alternative methods. Journal of Quantitative Linguistics 2013. 20 (3): 178–208).

### 12.6.2 Analysis Plans for Secondary Objectives

Adverse events will be summarized descriptively using frequencies and percentages of all captured toxicities and grades using CTCAE v.5 criteria. Adverse events leading to discontinuation of talazoparib, radiation, and/or atezolizumab will be recorded. Rates of side effects, and by location and site, will be reported, and will be compared across location or site type using chi-square tests or Fisher's exact tests, where appropriate. Progression-free survival, overall survival, duration of response, disease control rate, and time to progression will be estimated using the Kaplan-Meier method. DCR will be estimated as the proportion of all subjects with stable disease (SD), or partial response (PR), or complete response (CR) 8 weeks from the start of talazoparib until disease progression/recurrence out of the total number of patients. PFS, ORR, DOR, and DCR will be defined by both RECIST v1.1 and irRECIST criteria, based on the date of PD that will be used to determine duration, and will be analyzed separately by both criteria.

Progression-free survival is defined as length of time from start of talazoparib for the breast cancer metastases that a patient lives with the disease, but it does not get worse. Overall survival is defined as length of time from the start of talazoparib for the breast cancer metastases that patients diagnosed with the disease are still alive. Adherence will be measured by oral pill, intravenous infusion and radiation treatment compliance with prescribed systemic therapy and radiation dose and days of treatment. Patient-reported outcomes (PROs) including 1) Fatigue, as measured by MFI, actual scores and change from baseline; 2) Health Related Quality of Life, as measured by EORTC QLQ-C30, actual scores and change from baseline; 3) PROs and change in values over time will be summarized descriptively, using frequencies and percentages for categorical variables, and mean, median, standard deviation, interquartile range, and minimum/maximum for continuous variables. Best overall tumor response will be summarized by number and percentage of patients.

### 12.6.3 Analysis Plans for Exploratory Objectives

The influence of race on all above endpoints will be explored, as we anticipate at least 30% of our enrolled patients being African American based upon the patient demographics of the participating institutions. Additionally, we will explore the influence of BRCA and HRD status as well as previous lines of cytotoxic chemotherapy with or without immune therapy on response will be explored.

The incidence of biomarkers will be summarized using descriptive statistics. Comparisons of efficacy and safety endpoints between biomarker subpopulations may be performed. For each patient in the study, blood samples will be prospectively collected, evaluated and archived to support exploratory biomarker analysis. Exploratory biomarkers will be correlated with response. ctDNA will be measured pre- and 8 weeks post-atezolizumab, and B cell amount and type will be measured pre- and 2 weeks post-atezolizumab. ctDNA will be correlated with ORR using chi-squared tests (if ctDNA is dichotomized using cut points) or ANOVA, and will be correlated with PFS/OS using Cox regression and log-rank tests (if ctDNA is dichotomized using cut points). The proportional hazards assumption will be verified. Inflammatory cytokine measurements will be correlated with PROs using chi-squared tests, ANOVA, t-tests, and/or non-parametric equivalents such as Fisher's exact tests, Kruskal-Wallis, or Mann Whitney U tests, where appropriate. Longitudinal assessments will be modeled using generalized estimating

equations (GEE) or mixed modeling approaches, or withed paired approaches such as paired t-tests or McNemar's tests. The number and distribution of myeloid cells and IHC staining for SAMHD1 will be compared to ORR, PFS, and OS using chi-squared tests, ANOVA, t-tests, and log-rank tests. Cox regression will be considered. The number and types of B cells will be evaluated before and after radiotherapy using paired tests, such as paired t-tests and McNemar's tests. B cell distributions will be compared between patients who develop Grade 3 or higher toxicities an those who do not. Gene expression will also be compared between those who develop toxicities vs. those that do not, as well as responders vs. non-responders using chi-squared tests, ANOVA, and/or non-parametric equivalents, where appropriate.

### 12.6.4 Subgroup Analyses

Per-Protocol Population - All patients who receive and complete the first cycle of study treatment, have protocol-required post-baseline disease assessments and have no major protocol violations that would impact efficacy evaluations. Supportive analyses of efficacy endpoints will be performed on the per-protocol population.

## 12.7 Interim Analysis/Criteria for Stopping Study

Safety will be summarized using descriptive statistics. Atezolizumab will be held for most grade 2 irAEs per investigator's brochure and re-started after resolution of symptoms to grade 1 or better. However, we will stop the trial and deem the combination of talazoparib, radiation, and atezolizumab unsafe if any of the following occur:

1) Two of the first 3 patients enrolled develop grade 2 irAEs and are unable to resume systemic therapy within 8 weeks due to treatment-related toxicities OR
2) Two of the first 3 patients enrolled develop grade 3 or higher irAEs.

Additionally, the study will be stopped if 2 of the first 3 patients enrolled develop any one of the following:

1) Grade 3 or higher febrile neutropenia
2) Grade 3 thrombocytopenia with bleeding event
3) Grade 4 neutropenia, anemia, or thrombocytopenia
4) Any clinically meaningful Grade 3 non-hematologic event that leads to hospitalization or a medical intervention other than electrolyte or IVF support as deemed by the site investigator
5) Any grade 4 or higher non-hematological event with the exception of Grade 4 fatigue.

If these toxicities occur in 1 or fewer of the first 3 patients enrolled, the trial will proceed to assess an additional three patients. If 2 of the first 6 patients enrolled develop any of the above grade 2 irAEs and/or other Grade 3 or higher toxicities, the study combination of treatments will be deemed unsafe and the trial will be stopped. If one or fewer of the first 6 patients enrolled develop one of the above toxicities, the trial will continue to enroll the remaining patients until enrollment is complete.

### 12.7.1 Pre-Determined Criteria for Safety Concerns (n=18 gBRCA1/2 negative)

After all evaluable patients have been enrolled (18 gBRCA1/2 negative), we will deem the combination of talazoparib, radiation, and atezolizumab as unsafe if any of the following rates of toxicities are exceeded:

1) ≥ 40% of patients develop grade 3 or higher febrile neutropenia
2) > 40% of patients develop grade 4 neutropenia
3) > 40% of patients develop grade 4 leukopenia
4) > 30% of patients develop thrombocytopenia with bleeding event
5) > 20% of patients develop bone fracture following radiotherapy to the bone
6) > 35% of patients develop pneumonia
7) > 25% of patients develop Grade 3 or higher pneumonitis
8) > 5% of patients develop Grade 3 brachial plexopathy (assessed by LENT/SOMA or RTOG criteria) or Grade 3 spinal cord injury assessed by CTCAE version 5 due to radiation treatment to these areas
9) > 30% of patients develop other clinically meaningful non-hematologic Grade 3 toxicities (excluding neutropenia and leukopenia) that leads to hospitalization or a medical intervention other than electrolyte or IVF support not mentioned above and/or
10) > 40% of patients develop Grade 4 neutropenia, anemia, or thrombocytopenia or any grade 4 or higher non-hematological event with the exception of Grade 4 fatigue.

# 13 TRIAL MANAGEMENT

## 13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Emory Winship Cancer Institute's DSMP.

HCRN oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee according to Emory Winship Cancer Institute DSMP.

## 13.2 Emory Winship Cancer Institute Data Safety Monitoring Committee

HCRN will provide the following for the Winship Cancer Institute DSMC to review:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The Winship Cancer Institute DSMC will review study data annually. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

### 13.3 Data Quality Oversight Activities by HCRN

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

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 be performed as necessary. During onsite monitoring visits, 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 Genentech, Pfizer 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 Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), 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. Select 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 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 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, Genentech, 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.

## 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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# 17 APPENDIX I: 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.<br>• Re-evaluate on serial imaging.<br>• Consider patient referral to pulmonary specialist. |
| Pulmonary event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.<br>• Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• For recurrent events, treat as a Grade 3 or 4 event. |
| Pulmonary event, Grade 3 or 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Bronchoscopy or BAL is recommended.<br>• Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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 the equivalent of ≤ 10

mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the site investigator and 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-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the site investigator (or an appropriate delegate) and the sponsor-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.<br>• Monitor LFTs until values resolve to within normal limits. |
| Hepatic event, Grade 2 | • All events<br>• Monitor LFTs more frequently until return to baseline values.<br><br>**Events of > 5 days' duration**<br>• Withhold atezolizumab for up to 12 weeks after event onset. a<br>• Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• 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<br>• Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.<br>• Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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.<br>• Initiate symptomatic treatment.<br>• Endoscopy is recommended if symptoms persist for > 7 days.<br>• Monitor closely. |
| Diarrhea or colitis, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. a<br>• Initiate symptomatic treatment.<br>• Patient referral to GI specialist is recommended.<br>• For recurrent events or events that persist >5 days, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• 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<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• 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.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• 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<br>• Refer patient to GI specialist for evaluation and confirmation biopsy.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH weekly. |
| Symptomatic hypothyroidism | • Withhold atezolizumab.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH weekly.<br>• Consider patient referral to endocrinologist.<br>• Resume atezolizumab when symptoms are controlled and thyroid function is improving. |
| Asymptomatic hyperthyroidism | **TSH ≥ 0.1 mU/L and < 0.5 mU/L:**<br>• Continue atezolizumab.<br>• Monitor TSH every 4 weeks.<br><br>**TSH < 0.1 mU/L:**<br>• Follow guidelines for symptomatic hyperthyroidism. |
| Symptomatic hyperthyroidism | • Withhold atezolizumab.<br>• Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.<br>• Consider patient referral to endocrinologist.<br>• Resume atezolizumab when symptoms are controlled and thyroid function is improving.<br>• Permanently discontinue atezolizumab. c |
| Symptomatic adrenal insufficiency, Grade 2−4 | • Withhold atezolizumab for up to 12 weeks after event onset. a<br>• Refer patient to endocrinologist.<br>• Perform appropriate imaging.<br>• 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.<br>• If event resolves to Grade 1 or better and patient is stable on |

| | |
|---|---|
| | replacement therapy, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c] |
| Hyperglycemia, Grade 1 or 2 | • Continue atezolizumab.<br>• Initiate treatment with insulin if needed.<br>• Monitor for glucose control. |
| Hyperglycemia, Grade 3 or 4 | • Withhold atezolizumab.<br>• Initiate treatment with insulin.<br>• Monitor for glucose control.<br>• 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<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• 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.<br>• Initiate hormone replacement if clinically indicated.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c<br>• For recurrent hypophysitis, treat as a Grade 4 event. |
| Hypophysitis (pan-hypopituitarism), Grade 4 | • Permanently discontinue atezolizumab c<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• 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.<br>• 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.<br>• Patient referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If symptoms persist, treat as a Grade 2 event. |
| Ocular event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Patient referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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]<br>• Refer patient to ophthalmologist.<br>• Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.<br>• 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]<br>• Refer patient to cardiologist.<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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**

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (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.

**Management Guidelines for Infusion-Related Reactions**

| Event | Management |
|---|---|
| IRR, Grade 1 | • Reduce infusion rate to half the rate being given at the time of event onset.<br>• After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.<br>• If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate. |
| IRR, Grade 2 | • Interrupt atezolizumab infusion.<br>• Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen).<br>• After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.<br>• For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs. |
| IRR, Grade 3 or 4 | • Stop infusion.<br>• Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen).<br>• Permanently discontinue atezolizumab and contact Medical Monitor. a |

IRR = infusion-related reaction.

[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 according to institutional guidelines and the above table. In the case of Grade 3 or 4 IRRs, guidance from the Medical Monitor is highly recommended.

**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 2 | • Continue atezolizumab.<br>• Monitor amylase and lipase weekly.<br>• For prolonged elevation (e.g.,> 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. |
| Amylase and/or lipase elevation, Grade 3 or 4 | • Withhold atezolizumab for up to 12 weeks after event onset. a<br>• Refer patient to GI specialist.<br>• Monitor amylase and lipase every other day.<br>• If no improvement, consider treatment with 1−2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c<br>• 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<br>• Refer patient to GI specialist.<br>• 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.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c<br>• For recurrent events, permanently discontinue atezolizumab. c |
| Immune-related pancreatitis, Grade 4 | • Permanently discontinue atezolizumab. c<br>• Refer patient to GI specialist.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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).

**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. 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.<br>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines). |
| Dermatologic event, Grade 2 | • Continue atezolizumab.<br>• Consider patient referral to dermatologist.<br>• Initiate treatment with topical corticosteroids.<br>• 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<br>• Refer patient to dermatologist for evaluation and, if indicated, biopsy.<br>• 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.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• 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:<br>Withhold atezolizumab for suspected Stevens Johnson syndrome or toxic epidermal necrolysis.<br>Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.<br>Follow the applicable treatment and management guidelines above.<br>• 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.<br>• Investigate etiology. |
| Immune-related neuropathy, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Investigate etiology.<br>• Initiate treatment as per institutional guidelines.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• 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]<br>• Initiate treatment as per institutional guidelines. |
| Myasthenia gravis and Guillain-Barré syndrome (any grade) | • Permanently discontinue atezolizumab. [c]<br>• Refer patient to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• 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]<br>• Refer patient to neurologist.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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.<br>• 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<br>• Refer patient to renal specialist.<br>• Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab. b<br>• 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.<br>• Refer patient to renal specialist and consider renal biopsy.<br>• Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines |
| Immune-related myositis, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onseta and contact site investigator.<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines<br>• 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.<br>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent<br>• If event resolves to Grade 1 or better, resume atezolizumab.b<br>• 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 onseta and contact site investigator.<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines |

| | |
|---|---|
| | • Respiratory support may be required in more severe cases<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab.b<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact HCRN. c<br>• For recurrent events, treat as a Grade 4 event |
| Immune-related myositis, Grade 4 | • Permanently discontinue atezolizumab and contact site investigator.c<br>• Refer subject to rheumatologist or neurologist<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• 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).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

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 < $100 \times 10^9$/L (100,000/µL)
    - ANC < $1.0 \times 10^9$/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 ≤ $181 \times 10^9$/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 14.

**Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome**

| Event | Management |
|---|---|
| Suspected HLH or MAS | • Permanently sponsor-investigator.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy.<br>• If event does not respond to treatment within 24 hours, contact sponsor-investigator and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

**IMMUNE-MEDIATED PERICARDIAL DISORDERS**

The following recommendations will be included in the updated atezolizumab Investigator's Brochure (IB) and study protocols for immune-mediated pericardial disorders:

- The diagnosis of immune-mediated pericarditis should be considered in all patients presenting with chest pain.
- The diagnosis of immune-mediated pericardial effusion and cardiac tamponade should be considered in all patients presenting with chest pain associated with dyspnea or hemodynamic instability.
- Cardiac tamponade should be treated as a medical emergency and consultation with a cardiologist should be sought for further management.
- Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone 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.
- Atezolizumab should be withheld for patients with suspected immune-mediated pericardial disorders.
- Atezolizumab should be permanently withdrawn for any grade confirmed immune-mediated pericardial disorders.
- Caution should be used when considering the use of atezolizumab in a patient experienced a pericardial disorder on prior treatment with other immune-stimulatory anticancer agents.

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# 19. APPENDIX II: MANAGEMENT OF RADIATION-SPECIFIC ADVERSE EVENTS

Toxicities associated or possibly associated with radiation treatment should be managed according to standard medical practice.

Lung Injury

Pneumonitis due to radiation may occur weeks to months after treatment and is caused by inflammation of the end bronchioles and alveoli. Radiation oncologists will be expected to participate in the care and monitoring of enrolled patients for this symptom per standard of care. Patients reporting fever, shortness of breath, dry cough, and/or chest pain should be immediately evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. For severe cases, systemic steroids, bronchodilators, and pulmonary hygiene may be prescribed. Concurrent infections should be treated with antibiotics. Radiation fibrosis is a late manifestation of radiation lung injury.

For patients with lung (central or peripheral) and/or mediastinal/cervical lymph node metastases to be treated with radiation, corticosteroid premedication can be used at the discretion of the treating oncologist (in which case, its use needs to be reported.

Gastrointestinal/Esophageal Injury

Radiation may cause esophagitis or dysphagia, gastritis, enteritis, or colitis which typically resolves within a few weeks of radiation. It may also cause permanent injury, although infrequent at the proposed radiation treatment doses, which manifests as dysphagia with stenosis or esophageal, gastric, or intestinal ulceration with perforation in the extreme cases. Any of these toxicities must be clearly documented.

For patients with liver and/or abdominal-pelvic metastases (as well as any other patient at the discretion of the treating oncologist) anti-emetics may be given prior to each fraction of SBRT to prevent nausea.

Analgesics may be given to help with esophagitis.

Antidiarrheal medication as indicated may be used for symptomatic diarrhea.

Cardiac and pericardial Injury

Although uncommon at the proposed radiation doses on this protocol, radiation treatment to the heart has been associated with pericarditis, endocarditis, coronary artery disease, hypertension, myocardial infarction, and heart failure.

Assessments of heart function (e.g. Echo or MUGA) may be helpful prior to radiation to lesions within 2cm of the heart to determine impact of radiation on heart function. Referral to a cardiologist can help manage potential risk factors for heart disease.

Kidney Injury
Radiation may cause kidney injury but not typically at the doses prescribed on this protocol. Assessments of kidney function prior to radiation may be used to monitor for early signs of renal injury. Referrals to a nephrologist to help with the management of renal injury may be indicated.

Spinal injury
Radiation can cause myelitis which manifests as paresthesia, sensory changes, and motor weakness including paralysis. Because there is no effective treatment for myelitis, it is critical to prevent and avoid injury to the spinal cord. Corticosteroids may help with symptoms.

Osseous injury
Pathologic fractures and vertebral body compression fractures are extremely uncommon (<15%) at the proposed radiation doses of this protocol. Fractures of bones treated on this protocol will be reported immediately to the study monitor and study PI, Dr. Mylin Torres.

Pathologic fractures may be treated by vertebroplasty, kyphoplasty or surgical intervention.

Alopecia, erythema, desquamation are common side effects from radiation for osseous metastasis. Edema, pain, and neuralgia may be additional side effects of the treatment.

Erythema/desquamation may be managed with emollients, lotions/creams and/or silvadene cream.

Pain
Analgesic premedication to avoid general discomfort during simulation and treatment is recommended when appropriate.

## 20. APPENDIX III

For patient images stored on a PACS system at the participating institution or site, these images can be sent to Velocity in DICOM format where a research database will be used that does not contain any PHI, only the subject identifier number. Images from the clinical database will be saved to a directory, anonymized using a commercial anonymizer available in the Emory Department of Radiation Oncology (Velocity Anonymize, Varian Medical Solutions), and then uploaded in the research system. The anonymization procedure takes about 10 minutes to complete.

The research server is ideally suited for such projects as it replicates the clinical software environment but has its own database holding project-specific datasets. In addition, the research station has installed the Eclipse Advanced Scripting Programming Language (ESAPI) where researchers can write code in C# to create customized software scripts to extract and analyze patient data according to a project's design. For analysis, we will re-use a script created in the frame of previous research to automatically output plan quality measures to an Excel file for statistical processing. Extracted measures are plan indices such as the conformity, homogeneity and gradient indexes, dose statistics inside targets and critical structures, complete dose-volume histogram graphs, standard constraints values as well as any user-defined DVH points in any either absolute or relative formats for the dose or volume. With an extended version of the script, we can extract radiomics measures such as image features, statistics, and textures. These radiomics features can be extracted from either the patient's CT dataset or the plan's dose distribution. Extracted features also include segmentation characteristics such as the volume, area and tortuosity of each structure in the plan. Once imported in the research database, data received from the participating institutions will be processed with scripts to generate measures for statistical analysis.

If there are any questions regarding this process, please contact Edi Schreibmann, eschre2@emory.edu, 404-778-5667.

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