# Phase Ib/II study to evaluate safety and tolerability of neoadjuvant nivolumab and chemotherapy in patients with localized triple-negative breast cancer

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Nivolumab
SOC neoadjuvant chemotherapy
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**Phase Ib/II study to evaluate safety and tolerability of cabiralizumab in combination with nivolumab and neoadjuvant chemotherapy in patients with localized triple-negative breast cancer**

**Protocol Revision History**

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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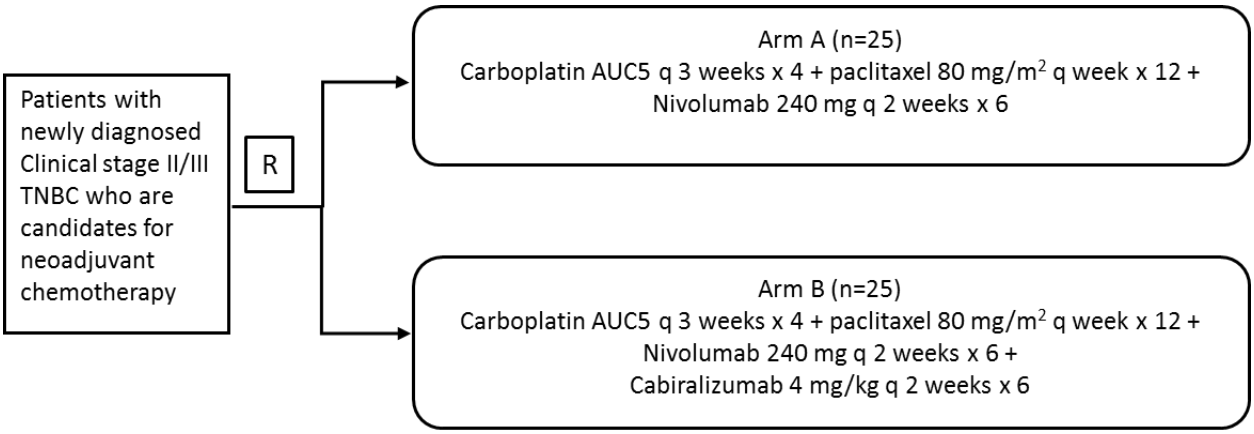
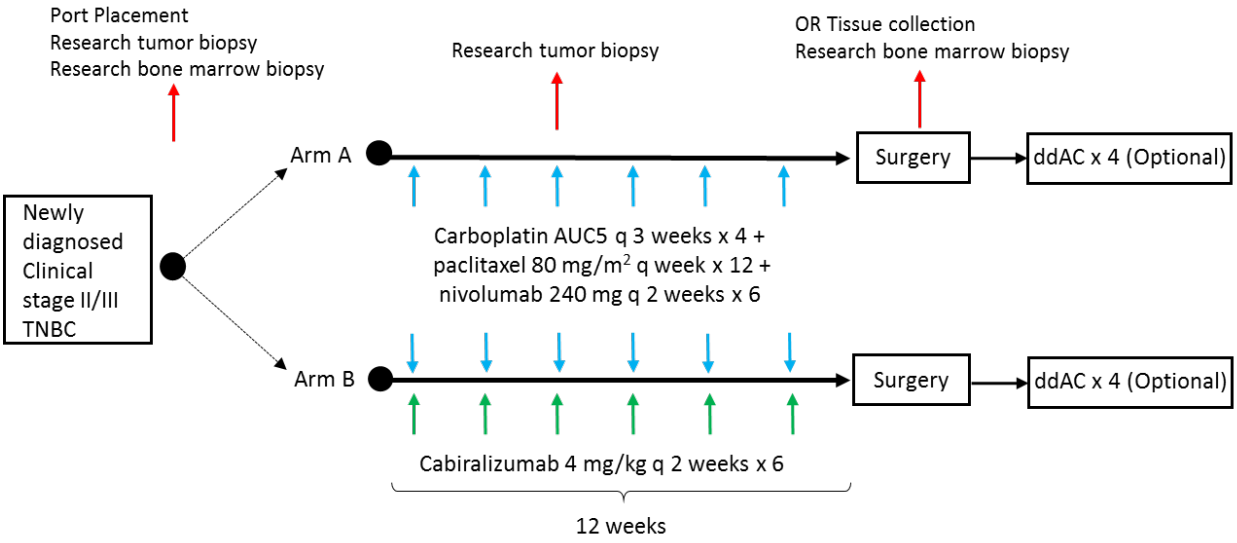
**PROTOCOL SUMMARY**

| | |
|---|---|
| **Title:** | Phase Ib/II study to evaluate safety and tolerability of neoadjuvant nivolumab and chemotherapy in patients with localized triple-negative breast cancer |
| **Study Description:** | The hypothesis of this study is that on-treatment tumor associated macrophages (TAMs) and tumor infiltrating lymphocytes (TILs) will improve (reduced TAMs, increased TILs) following neoadjuvant nivolumab with chemotherapy.<br><br>In this study, a safety lead-in of 12 eligible patients with clinical stage II/III TNBC will be randomized on a 1:1 ratio to receive neoadjuvant chemotherapy and nivolumab with or without cabiralizumab. Following the activation of Amendment 7, an additional 19 patients will be enrolled who will all receive neoadjuvant chemotherapy and nivolumab (cabiralizumab will not be given). |
| **Objectives:** | Primary Objective:<br>1. Safety lead-in: To investigate if the combination of neoadjuvant chemotherapy with nivolumab +/- cabiralizumab is safe in patients with TNBC.<br>2. To compare on-treatment TAMs and TILs against their baseline levels in patients with newly diagnosed stage II/III TNBC treated with neoadjuvant nivolumab + chemotherapy.<br><br>Secondary Objectives:<br>1. To estimate the pathological complete response (pCR) rate in patients with newly diagnosed stage II/III TNBC treated with neoadjuvant nivolumab + chemotherapy.<br>2. To determine recurrence-free survival (RFS).<br>3. To estimate grade 3 or higher treatment-related adverse event rate.<br>4. To compare the percent change of TAMs and TILs between patients who achieve pCR vs. those who do not.<br><br>Exploratory Objectives:<br>1. To evaluate disseminated tumor cell (DTC) gene signature elimination in the bone marrow after neoadjuvant treatment and correlation with pCR and prognosis.<br>2. To evaluate potential biomarkers of response to NAC + nivolumab +/- combination with cabiralizumab in patients with newly diagnosed TNBC. Potential biomarkers include baseline TAMs and/or TILs percentage, baseline PD-L1 expression in the tumor and tumor infiltrating immune cells, CSF-1R+. These biomarkers will be correlated with pathologic complete response.<br>3. To compare the difference in the immune cell infiltration and cytokine expression in the biopsied tumors of patients with |

| | |
|---|---|
| | TNBC before and after treatment with the combination of NAC plus nivolumab.<br>4. To correlate changes in the immune infiltrate with clinical responses to treatment with the combination of NAC plus nivolumab and clinical outcomes (pCR, RFS) following treatment.<br>5. To compare the difference in ctDNA response in patients who achieve pCR vs. patients who do not achieve pCR. |
| **Endpoints:** | Primary Endpoints:<br>The primary endpoint for the safety lead-in is toxicity by CTCAE v 5.0.<br><br>The co-primary endpoints are percent change of on-treatment TAMs from baseline and percent change of on-treatment TILs from baseline (stromal TIL score is defined as the percentage of tumor stroma area that was occupied by mononuclear inflammatory cells).<br><br>Secondary Endpoints:<br>- pCR rate<br>- AEs, especially grade 3 or higher treatment-related AE rate<br>- Recurrence-free survival defined from time of surgery to the earliest of time of recurrence, time to development of a 2nd cancer, time of death from any cause. |
| **Study Population:** | 31 women of any race and ethnicity newly diagnosed with clinical stage II or III triple-negative breast cancer will be enrolled to this study |
| **Phase:** | Ib/II |
| **Description of Sites / Facilities Enrolling:** | This study will be open at Siteman Cancer Center at Washington University School of Medicine. |
| **Description of Study Intervention:** | The neoadjuvant chemotherapy (NAC) being given on this study is paclitaxel 80 mg/m$^2$ IV weekly with carboplatin AUC 5 IV every 3 weeks for a total of 12 weeks. Nivolumab will be given with the chemotherapy at a dose of 240 mg IV every 2 weeks for 12 weeks. Patients who are randomized to the cabiralizumab arm will receive it with NAC plus nivolumab at a dose of 4 mg/kg IV every 2 weeks for 12 weeks. |
| **Study Duration:** | 88 months (24 months for accrual + 4 months for participation + 60 months for follow-up) |
| **Participant Duration:** | Neoadjuvant treatment will take place over the course of 12 weeks. The standard of care surgery and possible standard of care adjuvant therapy will occur as part of the patient's routine care and not as part of enrollment to this study. Follow-up will continue for 5 years after surgery. Total expected participant duration is approximately 64 months. |

## SCHEMA




The first six patients randomized to each arm will be part of a safety run-in. The allocation to an arm will pause after enrollment of the sixth patient to that arm until all six patients in that arm have completed all 12 weeks of treatment and have passed the toxicity monitoring period (4 weeks after last dose or until surgery whichever occurs first.

With the conclusion of the safety run-in and the activation of Amendment 7, randomization is discontinued and all patients will enroll in Arm A (SOC chemo + nivolumab).

## SCHEDULE OF ACTIVITIES

There is a 21-day window for screening and +/- 1-day window for all assessments and procedures.

| | **Screening** | **W1** | **W2** | **W3** | **W4** | **W5** | **W6** | **W7** | **W8** | **W9** | **W10** | **W11** | **W12** | **Surgery[10]** | **Post-Op F/U** | **F/U[6]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | | | | | | | | |
| Height[14] | X | | | | | | | | | | | | | | | |
| H&P, ECOG PS | X[11] | X | | X | | X | | X | | X | | X | | | X | |
| CBC | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| CMP | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| TSH, T3, T4 | | X | | X | | X | | X | | X | | X | | | | |
| INR, aPTT | X | | | | | | | | | | | | | | | |
| TB test[13] | X | | | | | | | | | | | | | | | |
| Cortisol | | X | | X | | X | | X | | X | | X | | | | |
| Lipase | X | X | | X | | X | | X | | X | | X | | | | |
| Urinalysis | X | X | | | | X | | | | X | | | | X[8] | | |
| Pregnancy test[1] | X | X | | | | X | | | | X | | | | X[8] | | |
| 12-lead EKG | X | X | | | | X | | | | X | | | | X[8] | | |
| CT scan (chest) | X[12] | | | | | | | | | | | | | | | |
| Randomization | X[9] | | | | | | | | | | | | | | | |
| Carboplatin | | X | | | X | | | X | | | X | | | | | |
| Paclitaxel | | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Nivolumab | | X | | X | | X | | X | | X | | X | | | | |
| Carbiralizumab[2] | | X | | X | | X | | X | | X | | X | | | | |
| Research breast biopsy[15] | X[9] | | | | | X[3] | | | | | | | | X[4] | | X[7] |
| Research bone marrow biopsy[15] | X[9] | | | | | | | | | | | | | X | | X[7] |
| Research blood draw[15] | X[9] | | X[3] | X[3] | | X[3] | | | | | X[3] | | | X[16] | X | X[7] |
| AE assessment | | X ---------- X[5] | | | | | | | | | | | | | | |
| Concomitant medications | | X ---------- X | | | | | | | | | | | | | | |
| Progression and survival | | | | | | | | | | | | | | | | X |

1. Women of childbearing potential only
2. If randomized to Arm B; note that after completion of the safety run-in and with the activation of Amendment 7, all patients enrolled thereafter will be treated in Arm A.
3. Prior to treatment

4. From surgical specimen
5. Until 100 days after last treatment or day of surgery, whichever is first
6. Follow-up will be at 6 months and 1 year post-surgery, and then on a yearly basis thereafter for an additional 2 years (3 years total). Patients who do not undergo surgery will be followed for survival only.
7. At time of recurrence only – OPTIONAL
8. Within 2 weeks prior to day of surgery
9. To occur after consent
10. Within 4-8 weeks after last dose of study treatment (but may be delayed depending on the availability of the surgeon)
11. Includes 2D measurements of breast tumor
12. Within 4 weeks prior to the start of therapy
13. 21 day screening window applies to when TB test is read, not placed
14. Use for dosing
15. Refer to Section 9.1.1 for exception to specimen collection
16. Collect up to 7 days prior to day of surgery

# 1.0 INTRODUCTION

## 1.1 Rationale to conduct a study in patients with localized Triple negative breast cancers

Breast cancer is a major public health problem. In the United States (US), 1 out of 8 women will be diagnosed with breast cancer in their life time [1]. A total of 268,670 new breast cancer cases and 41,400 deaths are expected to be attributed to BC in the year 2018 [2]. Since the majority of breast cancer cases are diagnosed at an early stage (I – III), relapse of early stage disease accounts for the majority of breast cancer deaths [1]. The neoadjuvant setting has become an important research tool in drug development and in studying mechanisms of resistance. Response to neoadjuvant chemotherapy measured by pathologic complete response (pCR) rate, and post-chemotherapy residual disease burden has been shown to correlate with long-term outcomes [3-5]. Triple negative breast cancer (TNBC) is immunohistochemically defined by the lack of estrogen receptor (ER), and progesterone receptor (PR) expression, as well as lack of overexpression/amplification of human epidermal growth factor receptor 2 (HER2). Given the lack of clinically meaningful therapeutic targets in TNBC, limited treatment options are available for TNBC, and patient outcomes are typically poor. Pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) is associated with improved outcomes in TNBC [5,6]. Standard anthracycline-taxane containing NACT leads to pCR in 25% to 40% of TNBC [7,8]. Platinum-based neoadjuvant regimens have yielded superior pCR rates (about 50%) [8-10]. The optimal chemotherapy regimen remains unclear and chemo-resistant disease is a clinical challenge. The majority of patients with TNBC still suffer from dismal clinical outcomes including early relapse and metastatic spread. Therefore, developing optimal therapeutic strategies for the treatment of TNBC is an unmet need.

Tumor infiltrating myeloid cells including tumor-associated macrophages (TAMs) are linked to immune checkpoint inhibitor resistance. Reducing TAMs number is a promising strategy to enhance PD-1 inhibitors effectiveness due to its marked effect on tumor microenvironment. The evidence that TAMs result crucial in modulating the expression and activity of immune checkpoints suggest that combined TAM-centered strategies could maximize the efficacy of anti-PD-1 agents in breast cancer [11].

We propose a study to investigate the safety and preliminary clinical activity of cabiralizumab, a CSF1R inhibitor, in combination with nivolumab and neoadjuvant chemotherapy in patients with triple-negative BC. The effect of CSF1R targeting in combination with nivolumab and chemotherapy on the tumor immune microenvironment, peripheral blood immune cell and cytokine profile, and bone marrow microenvironment of breast cancer patients is unknown, as is the aim of our correlative studies in this proposed study.

**We aim to prove that cabiralizumab will induce a significant reduction of TAMs (CD68+/CD163+) and CSF-1R+ cells in on-treatment biopsies analyzed after 4 weeks**

**of therapy and this change is correlated with increasing TILs and better clinical outcomes.**

### 1.2 Rationale for immunotherapy in TNBC

Accumulating evidence is supporting the study of immunotherapy in combination with chemotherapy in breast cancer. TNBC is characterized by high genomic instability and high mutational burden with abundant infiltrating immune cells [12]. Multiple studies are focusing on combining programmed cell death-1/programmed death ligand-1 (PD-1/PD-L1) antagonists with chemotherapy in different settings and early data are encouraging. The recently published Impassion130 phase 3 trial demonstrated that atezolizumab plus nab-paclitaxel, compared to nab-paclitaxel alone, prolonged progression-free survival (7.2 months v 5.5 months, respectively) in patients with metastatic TNBC. Importantly, this benefit is driven by the patients with positive PD-L1 expression in immune cell infiltrates [13]. In early TNBC, phase I/II studies have reported increased pCR rates with PD-1/L1 blockade in combination with neoadjuvant chemotherapy. The I-SPY 2 trial demonstrated that pCR rates increased from 22.3% to 62.4% by adding neoadjuvant pembrolizumab to paclitaxel followed by anthracycline-based chemotherapy, which represents an approximately 40% improvement in pCR compared with standard chemo- therapy alone [14]. The KEYNOTE-173 trial showed a remarkably increased pCR rate from 60% to 90% in high-risk patients by combining pembrolizumab with paclitaxel or conventional chemotherapy according to the physician's discretion [15]. More recently, the GeparNuevo study presented at ASCO 2018 showed that the addition of durvalumab to neoadjuvant chemotherapy increases the pCR rate numerically in primary TNBC patients (53% vs 44%; p=0.287) [16]. The encouraging results from these early studies have led to launch several phase 3 clinical trials of PD-1/L1 checkpoint inhibition plus neoadjuvant chemotherapy in TNBC (KEYNOTE-522, NSABP B-59, IMPassion 030). These results are encouraging and ongoing efforts are to improve the effectiveness of immunotherapy by overcoming the molecular mechanisms that drive resistance to checkpoint blockade in breast cancer.

### 1.3 Rationale to target tumor-associated macrophages (TAMs) in breast cancer

The tumor microenvironment plays an important role in breast cancer progression. Among the many cell types associated with the tumor microenvironment, macrophages are among the most influential for breast cancer progression by promoting angiogenesis, tumor growth and metastasis [17-19]. Tumor-associated macrophages (TAMs) are elevated in many tumors including breast cancer. Macrophages are an important component of the mammary gland stroma and facilitate normal mammary gland development. Resident macrophages in the adult mammary gland play crucial roles in homeostasis and modulation of inflammation. In the breast cancer microenvironment, TAMs are among the most important regulators of tumor progression.

Immune cells represent a major component of TNBC microenvironment [20] and have been identified as potential prognostic factors in these patients [21]. TAMs constitute a major leukocyte population infiltrating tumors that originate from circulating blood monocytes differentiating into macrophages after their extravasation into tissues. TAMs are recruited

into the BC microenvironment and, in response to several stimuli, undergo M1 (classical) or M2 (alternative) activation [22,23]. Breast cancer cells have been shown to secrete factors that promote macrophage polarization towards M2 status. High number of CD163+ M2-macrophages was strongly correlated with higher proliferation, poorer differentiation, HR negativity and histological ductal type [24]. Several mediators are involved in M2 polarization, including IL-4, IL-10, Transforming Growth Factor-β (TGF-β) and Macrophage-Colony Stimulating Factor (M-CSF) [25]. TNBC secretes more Granulocyte-Colony Stimulating Factor (G-CSF) than other BC histologies, thus promoting M1 cell skewing to M2 status [26]. Medrek et al. stained M2 macrophages for CD163 and reported that these cells were more present in TNBC and basal-like BC [27]. Furthermore, CD163+ cells were directly associated with HR negativity and TNBC histology and inversely correlated with Luminal A subtype. More recently, Klingen et al. have confirmed these data reporting a strong correlation between high CD163 count and aggressive features such as vessel invasion in nonluminal breast cancer [28]. Moreover, CD204 is emerging as a marker to identify TAMs in breast cancer and a high number of CD204+ TAMs correlates with worse prognoses in this setting [29]. Interestingly, patients with TNBC after surgery showed augmented number of TAMs and expression levels of IL-6, which is directly implicated in TNBC angiogenesis and cell migration [30], and Chemokine (C-C motif) Ligand 5 (CCL5), which is involved in TNBC cell invasiveness and dissemination [31{Wang, 2016 #105}]. In TNBC, TAMs exert their immunosuppressive functions by several mechanisms that include: (1) the secretion of inhibitory cytokines; (2) the reduction of effector functions of TILs; (3) the promotion of Regulatory T cell (Treg) development; (4) the production of reactive oxygen species.

Colony-stimulating factor-1 (CSF-1) is required to recruit macrophages into the mammary gland and tumor microenvironment. The bone marrow releases monocytes and other myeloid derived suppressor cells (MDSCs, the precursors of granulocytes, macrophages and dendritic cells) into the peripheral blood. Monocytes are ultimately recruited to the breast cancer microenvironment, by the influence CSF-1, where they become TAMs [27]. Multiple studies have demonstrated that TAM infiltration is associated with poor chemotherapy response and prognosis in breast cancer [32,33]. Treatment with neoadjuvant paclitaxel has been demonstrated to increase CSF-1 expression and elevate TAM infiltration in the breast cancer microenvironment [32]. Furthermore, high levels of TAM infiltration were associated with high histologic grade and high Ki-67 proliferation index in both hormone receptor-positive and hormone receptor-negative groups, and was an independent prognostic factor for poor disease-free survival in hormone-receptor positive breast cancer [34]. All the above, provides a rationale to target TAMs with CSF-1 receptor inhibition in breast cancer

### 1.4 Rationale to combine checkpoint inhibitors with CSF-1R inhibitor and chemotherapy

It is well accepted that checkpoint blockade alone is an insufficient therapeutic approach in most breast cancers. Therefore, current efforts are focused on developing immunotherapy combinations that convert nonresponders to responders, deepen those responses that do occur and overcome resistance to immunotherapy [12]. In metastatic

TNBC, the combination of atezolizumab with chemotherapy led to improved outcomes and demonstrated that combining checkpoint inhibitors with chemotherapy is feasible and effective in this subgroup of breast cancers. However, the clinical benefit was mostly limited to tumors that had a pre-existing immune response evident by the PD-L1 positive immune cells [13]. One explanation for the modest response rates to immunotherapy in breast cancer is that PD-1/L1 blockade requires pre-existing immune "recognition" of the tumor and that some tumor types are less naturally recognizable by the immune system due to either low antigenicity related to mutational load and/or a hostile tumor microenvironment [35].

TAMs have been shown to directly and indirectly modulate PD-1/PD-L1 expression in tumor environment [36,37]. TAMs are able to secrete several cytokines that mediate their immunosuppressive and pro-tumor activity in the tumor microenvironment. Among them, Interferon (IFN)-γ, IL-1β, TNF-α, TGF-β, IL-6 and IL-18 present key mediators of TAM functions[38]. Indeed, TAMs can induce the expression of PD-L1 by the secretion of IFN-γ via Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) and the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways [39]. Recently, IFN-γ-related mRNA profile has been proposed as a predictor of clinical response to PD-1 blockade[40]. TGF-β is a multifunctional cytokine that is involved in generating Tregs and supporting their suppressive activity against cytotoxic T cell (CTL) effector function in the tumor microenvironment in mouse models[41,42]. TGF-β can also increase the suppressive activity of TAMs by inducing their polarization to M2 phenotype and induce the upregulation of PD-L1, leading to tumor escape [43]. Furthermore, TAMs have been shown to reduce the effector activity of TILs. In TNBC patients, the presence of high levels of TILs has been significantly correlated with a better prognosis [44]. Patients with TNBCs with combined low-TILs and high-PD-L1 expression showed poor prognosis in the preoperative systemic therapy setting [45]. TAMs are implicated in promoting the activity of Tregs. PD-L1 and FOXP3 +Tregs seems to work synergistically and their overexpressions induce cancer immune evasion in BC [46]. Based on these findings, combined strategies aimed at blocking PD-1 and depleting Tregs should be investigated in these patients.

Colony-stimulating factor 1 (CSF1) play a key role in monocyte recruitment and TAM generation. Ding et al. revealed that in vivo inhibition of CSF1 reduced TAM infiltration and tumor growth and progression[47]. These results indicate that CSF1 pathway inhibition may represent effective strategies to reduce TAM accumulation and, as a consequence, to modulate PD-1/PD-L1 expression in BC. Breast cancer mouse models with high levels of infiltrating myeloid cells, had lower infiltration of cancer-killing T-cells and, for this reason, were resistant to anti-PD-1 or anti-CTLA4 therapy. Cabiralizumab, a humanized IgG4 monoclonal antibody, binds to CSF-1 receptor (CSF-1R) and blocks cytokine signaling that is needed for TAM activation and survival, leading to TAM depletion. Targeting immunosuppressive TAMs within tumors with cabiralizumab may prevent immune evasion by cytotoxic T-cells. Tumor infiltrating myeloid cells including TAMs are linked to immune checkpoint inhibitor resistance, suggesting that cabiralizumab treatment may improve the efficacy of immune checkpoint blocking therapies in patients with high levels of TAMs infiltration. In addition, De Nardo et al, highlighted the importance of the CSF1/CSF1R signaling in the recruitment of TAMs in breast cancer and

further showed that CSF1R blockade can inhibit TAMs and enhance the activity of chemotherapy. Therefore, inhibiting the CSF1R with cabiralizumab to deplete immunosuppressive TAMs may be synergistic to PD-1 blockade.

The initial purpose of this study was to investigate the safety and preliminary clinical activity of cabiralizumab in combination with nivolumab and neoadjuvant chemotherapy in TNBC patients. However, with Amendment 7, the purpose of this study became investigating the safety and clinical activity of neoadjuvant nivolumab and chemotherapy in TNBC patients.

## 1.5 Cabiralizumab

(Note: following the conclusion of the safety lead-in and beginning with the implementation of Amendment 7, cabiralizumab is no longer given to patients enrolled to this study.)

CSF1R signaling plays a fundamental role in the differentiation, maintenance, trafficking, and function of monocytic lineage cells, including monocytes, macrophages, and osteoclasts. Cabiralizumab blocks the binding of CSF1 and IL34 to CSF1R, thus inhibiting downstream functions such as development and survival of monocytic lineage cells. Immunosuppressive TAMs are dependent on CSF1 for survival; a drug that inhibits CSF1R could limit the influence of TAMs on the tumor microenvironment and could be complementary and augment current cancer therapies (eg, checkpoint-based immunotherapies such as antibodies that target the programmed cell death protein 1 [PD1].

Cabiralizumab also referred to as BMS-986227-01, BMS-986227, or FPA008 is a recombinant, humanized IgG4 mAb that binds to human CSF1R. Binding of cabiralizumab to CSF1R antagonizes binding of CSF1 and IL34, the 2 ligands to CSF1R, thereby preventing activation of CSF1R. Cabiralizumab contains a single amino acid substitution in the hinge region to prevent hemi-dimer exchange. Cabiralizumab, is composed of 2 heavy chains and 2 light chains that targets human CSF1R. Cabiralizumab is produced from cell culture using a Chinese Hamster Ovary (CHO) cell line. The physical and chemical properties of cabiralizumab drug substance are summarized below:

**Physical and Chemical Properties of Cabiralizumab Drug Substance**

| | |
|---|---|
| BMS Number | BMS-986227-01 |
| Other names | BMS-986227; Cabiralizumab, Anti-CSF1R mAb, FPA008 |
| Molecular Weight | 148,910 Daltons |
| Appearance | Colorless to yellow liquid, clear to very opalescent |
| Solution | pH 6.2 to 7.0 |

**Cabiralizumab Clinical Safety:**

Cabiralizumab was evaluated in 1 completed study (Study FPA008001) and is currently being evaluated in 5 ongoing studies (Study FPA008002, Study FPA008003, Study

CA025001, Study CA025006, and Study CA028001). This section presents summarized and preliminary data from some of these studies. Across all studies, a total of 151 subjects were treated with cabiralizumab monotherapy, and 429 subjects were treated with cabiralizumab in combination with nivolumab, with or without chemotherapy.

Overall, cabiralizumab as monotherapy demonstrates a tolerable safety profile in subjects with malignancies and healthy volunteers. This is based on safety data from 151 subjects. The most frequent AEs (AST increased and blood creatine phosphokinase increased) are results for the specific MOA of cabiralizumab. The overall incidence of treatment related SAEs are infrequent. The combination of cabiralizumab and nivolumab appears to be tolerated based on data from 429 subjects. The safety profile appears similar to that of the individual components and the frequency and types of immune-mediated AEs appear similar across multiple types of tumors. Additionally, the combination of cabiralizumab and nivolumab with or without chemotherapy as evaluated in Study CA025006 appears to be tolerated.

Alteration in enzymes (eg, AST, ALT, and CK) in the absence of changes in bilirubin and periorbital edema have been observed across multiple trials as a consequence of the depletion of tissue-infiltrating macrophages mediated by cabiralizumab. Skin disoders have occurred across multiple trials. The specific algorithms developed for cabiralizumab provide extensive guidance to manage these events.

- **Study FPA008002 (Phase 1-Dose escalation):** In Phase 1 dose-escalation monotherapy, AEs considered by the investigator as related to cabiralizumab were experienced by 9 of 9 (100%) subjects. There were no Grade 5 treatment-related AEs experienced by any subject in Phase 1 monotherapy. those experienced by > 1 subject included periorbital edema and fatigue (6 [66.7%] subjects each); peripheral oedema (5 [55.6%] subjects); blood creatine phosphokinase increased (4 [44.4%] subjects); dry skin, facial edema, and pruritus generalized (3 [33.3%] subjects each); and ALT increased, AST increased, dermatitis, rash, and skin disorder (2 [22.2%] subjects each). In Phase 1 dose-escalation monotherapy, SAEs were experienced by 2 of 9 (22.2%) subjects. One subject experienced Grade 3 endocarditis, Grade 3 intervertebral discitis, and Grade 3 streptococcal sepsis. The other subject experienced Grade 2 hypertension and Grade 2 upper abdominal pain. All SAEs were determined to be not treatment related. In Phase 1 dose-escalation monotherapy, 3 of 9 (33.3%) subjects discontinued study treatment due to treatment-related AEs including skin disorder, blood creatine phosphokinase increased, and periorbital oedema (1 [11.1%] subject each). No deaths were reported in Phase 1 of this study.
- **Study FPA008003 (Phase 1a combination therapy):** As of 15-Jul-2019, in the Phase 1a combination therapy dose-escalation cohorts, AEs were experienced by 15 of 16 (93.8%) subjects treated. In the Phase 1a combination therapy dose-escalation cohorts, 2 (12.5%) subjects had Grade 5 events, which included respiratory failure and treatment-related pneumonitis (1 subject each). treatment-related AEs were experienced by 13 of 16 (81.3%) subjects. The most commonly reported (□ 3 subjects) treatment-related AEs included fatigue (8 [50%] subjects);

periorbital oedema (7 [43.8%] subjects); and rash, blood creatine phosphokinase increased, AST increased, rash maculopapular, pruritus, and pneumonitis (3 [18.8%] subjects each). There was 1 (25%) subject that experienced a Grade 5 treatment-related AE of pneumonitis. In the Phase 1a combination therapy dose-escalation cohorts, 7 of 16 (43.8%) subjects experienced at least 1 SAE. Treatment related SAEs occurred in 2 of 16 (12.5%) subjects and included Grade 5 pneumonitis (1 [6.3%] subject) and Grade 3 colitis (1 [6.3%] subject). No DLTs were reported in the Phase 1a dose-escalation combination therapy arm of this study. In the Phase 1a combination therapy dose-escalation cohorts, 3 of 16 (18.8%) subjects discontinued study treatment due to a treatment-related AE and included Grade 4 pneumonitis (1 [6.3%] subject), Grade 3 colitis (1 [6.3%] subject), and Grade 2 urticaria (1 [6.3%] subject).

- **Study CA025001: A Phase 1 Study of Cabiralizumab Administered Alone or in Combination with Nivolumab in Advanced Malignancies**. The administration of 4 mg/kg cabiralizumab + 3 mg/kg nivolumab with a Q2W interval presents a tolerable safety profile. Treatment-related AEs in the 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W cohort C1 were experienced by 7 of 7 (100.0%) subjects. The most commonly reported treatment-related AEs included AST increased (7 of 7 [100.0%] subjects), blood creatine phosphokinase increased (6 [85.7%] subjects), amylase increased and lipase increased (4 [57.1%] subjects), and blood ALP increased (3 [42.9%] subjects each). Treatment-related AEs in the 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W cohort C2 were experienced by 4 of 5 (80.0%) subjects. The most commonly reported treatment-related AEs included blood creatine phosphokinase increased (3 [60.0%] subjects) and amylase increased and AST increased (2 [40.0%] subjects each). There were no Grade 5 AEs experienced by any subject in monotherapy and combination therapy. Of the subjects treated with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W, 5 of 12 (41.7%) subjects experienced at least 1 SAE. Treatment-related SAEs occurred in 1 of 12 (8.33%) subjects. The subject experienced Grade 3 gastritis bacterial. None of the subjects treated in this study discontinued treatment due to a drug-related AE. One of 7 (14.3%) subjects treated with cabiralizumab monotherapy discontinued treatment due to an AE of Grade 2 deep vein thrombosis, which was not related to treatment. Two of 12 (16.7%) subjects treated with 4 mg/kg cabiralizumab + 3 mg/kg nivolumab Q2W due to Grade 5 AEs of cholangitis infective (C1) and plasma cell myeloma (C2), which were not related to treatment. No deaths due to treatment-related AEs were reported.
- **Study CA025006: A Phase 2 Study of Cabiralizumab Administered in Combination with Nivolumab with and without Chemotherapy in Subjects with Advanced Pancreatic Cancer.** The treatment of 4 mg/kg cabiralizumab Q2W and 480 mg nivolumab Q4W with or without gemcitabine and nab-paclitaxel or FOLFOX demonstrate a tolerable and manageable safety profile. Arm C of this study investigated cabiralizumab in combination with nivolumab and gemcitabine/Abraxane. Treatment-related AEs were experienced by 34 of 40 (85.0%) subjects in Arm C. The most commonly reported treatment-related AEs included AST increased and fatigue (16 [40.0%] subjects each); blood creatine phosphokinase increased and anemia (13 [32.5% subjects); ALT increased,

thrombocytopenia, and periorbital oedema (11 [27.5%] subjects each); platelet count decreased (9 [22.5%] subjects); nausea and neutropenia (8 [20.0%] subjects each); blood ALP increased, WBC count decreased, vomiting, rash, and decreased appetite (7 [17.5%] subjects each); and pruritus, rash maculo-papuloar, blood lactate dehydrogenase decreased, pyrexia, and diarrhea (6 [15.0%] subjects each). Treatment- related SAEs occurred in 9 of 40 (22.5%) subjects in Arm C. One subject experienced Grade 2 pneumonitis; 1 subject experienced Grade 3 acute kidney injury; 1 subject experienced Grade 3 thrombocytopenia; 1 subject experienced Grade 2 facial edema and Grade 2 peripheral edema; 1 subject experienced Grade 2 myositis and Grade 4 neutropenia; 1 subject experienced Grade 4 liver abscess; 1 subject experienced Grade 2 pneumonitis; 1 subject experienced Grade 1 pyrexia; and 1 subject experienced Grade 2 pyrexia. Fifty-six of 157 (35.7%) subjects died during the course of the study due to disease progression, 1 (0.6%) subject due to study drug toxicity, 2 (1.3%) subjects due to AE/SAE indicated death, 5 (3.2%) subjects due to "other," and 1 (0.6%) subject due to "unknown." Forty-one of 157 (26.1%) subjects died during the course of the study within 100 days of the last dose due to disease progression.

- ***Unexpected Life-threatening and/or Fatal Serious Adverse Reactions*** There were no unexpected life-threatening and/or fatal serious adverse reactions (SARs) experienced by subjects following cabiralizumab monotherapy exposure. The unexpected life-threatening and/or fatal SARs experienced by subjects following cabiralizumab plus nivolumab combination therapy with or without chemotherapy are shown in the following table obtained from the investigator brochure (version no. 07) :

**Table 5.5.7-1: Life-threatening and/or Fatal Serious Adverse Reactions with Cabiralizumab in Combination with Nivolumab with or without Chemotherapy (Number of Subjects Dosed = 429)**

| System Organ Class | Preferred Term | Frequency of all SARs | Occurrence of Life-Threatening SARs | Occurrence of Fatal SARs |
|---|---|---|---|---|
| Investigations | Blood Creatine Phosphokinase Increased | 9 (2.10%) | 1 (0.23%) | 0 |
| Respiratory, Thoracic and Mediastinal Disorders | Acute Respiratory Failure | 2 (0.47%) | 0 | 2 (0.47%) |
| | Respiratory Distress | 1 (0.23%) | 0 | 1 (0.23%) |
| Injury, Poisoning and Procedural Complications | Subdural Haematoma | 1 (0.23%) | 1 (0.23%) | 0 |
| Gastrointestinal Disorders | Pancreatitis | 4 (0.93%) | 0 | 1 (0.23%) |
| | Colitis | 4 (0.93%) | 1 (0.23%) | 0 |
| Infections and infestations | Sepsis | 3 (0.70%) | 0 | 1 (0.23%) |
| | Liver Abscess | 1 (0.23%) | 1 (0.23%) | 0 |
| | Fungal Infection | 1 (0.23%) | 0 | 1 (0.23%) |

### 1.6 Rationale to conduct this study in the neoadjuvant setting

Most early-phase drug development trials are conducted in patients with metastatic disease; however, this population may be the least amenable to response to immunotherapy because of larger tumor burden and/or treatment-related immune suppression. The following are additional points to support the conduction of this study in this population:

1. TNBC carries a poor prognosis with high risk of relapse and early time course of metastasis. Therefore, investigating novel agents/combinations in this setting is feasible.
2. Pathologic complete response to NACT and TILs are emerging as surrogates of prognosis in TNBC. Pre-surgical treatment allows for serial assessment of TILs, which may be useful for demonstrating favorable on-target treatment effects such as decreasing TAMs and expansion of effector T cells and within the tumor microenvironment by cabiralizumab.
3. The neoadjuvant setting allows evaluating if facilitating antitumor immunity will also target disseminated tumor cells (DTCs) in the bone marrow and increase the likelihood of long-term disease control. This study will collect pre-treatment blood, tumor and bone marrow to test for DTCs and evaluate the effects of immunotherapy on the microenvironment of DTCs which is novel. Our research team has developed methods to enrich, detect, and classify DTCs in breast cancer patients correlating the presence of DTCs with prognosis and response to anti-cancer treatments. The correlative work in this trial is heavily focused on exploring the biological and immunological basis for DTC dormancy, to understand the molecular heterogeneity of DTCs and to investigate the effects of immunotherapy on DTCs and their microenvironment.
4. Correlative studies will be conducted on serially collected blood, tumor and bone marrow specimens to explore the local and systemic impact of the intervention, with a goal of directly informing future studies.
5. During the study we will incorporate a safety lead in phase in which we will assess the safety of administering the combination of nivolumab, cabiralizumab and chemotherapy in early-stage TNBC.

Thus, we have chosen weekly paclitaxel plus carboplatin as the chemotherapy backbone to combine with immunotherapy for the patients with TNBC based on the results from the KEYNOTE-173 study (NCT02622074), a six-cohort phase Ib study of neoadjuvant platinum/taxane chemotherapy in combination with pembrolizumab in patients with locally advanced TNBC. In this study, six-cohorts were evaluated with different doses and schedules of taxanes and platinum in combination with pembrolizumab. The study sought to determine the safety and tolerability as well as establish a recommended phase II dose for further evaluation. The patients treated with the combination of paclitaxel 80 mg/m2 weekly with carboplatin (AUC 5 every 3 weeks) plus pembrolizumab had an ORR of 70% and there were no DTLs reported. The findings support the ongoing phase 3 KEYNOTE-522 trial, which is comparing this combination with placebo in this patient population. The ADAPT-TN trial demonstrated that an anthracycline-free regimen of nab-paclitaxel plus

carboplatin for 12-weeks had high efficacy and tolerability. Furthermore, those patients that achieved a pCR did not seem to benefit from additional anthracycline therapy in the adjuvant setting.

### 1.7 Rationale for tumor infiltrating lymphocytes (TILs) and pathologic complete response as endpoints

Tumor infiltrating lymphocytes (TILs), mainly the CD8 +T cells, have been identified and validated as a predictive and prognostic biomarker of long-term survival in TNBC treated with neoadjuvant chemotherapy [48,49]. In metastatic TNBC patients treated with atezolizumab, response rate and overall survival significantly correlated with the level of TILs [50]. Several retrospective studies of early TNBC demonstrated significantly worse survival outcomes in patients with high PD-L1 expression and a low number of TILs or a high ratio of PD-L1/CD8 expression [45,51,52]. On the contrary, immunogenic factors potentially involved in the expression of neoantigens positively correlated with higher TILs and a more favorable prognosis [53,54]. All the above supports the use of TILs as a predictive and prognostic immune biomarker [55,56]. Pathological complete response (pCR)- defined as complete absence of disease in the breast and lymph nodes- after neoadjuvant chemotherapy (NACT) is associated with improved outcomes in TNBC [5,6]. Therefore, pCR has been used as a primary endpoint in most neoadjuvant trials in TNBC. It is important to acknowledge that even though there is a clear correlation between pCR with chemotherapy and long-term outcomes in TNBC, there is uncertainty on how clear the correlation is with immune therapy combinations. Early data from the Keynote-173 study of pembrolizumab plus chemotherapy reported 12-month event free survival rates of 100% among patients who achieved pCR and 88% (90% CI, 71-95) among those who did not (Schmid P, et al. Abstract PD5-01. Presented at: San Antonio Breast Cancer Symposium; Dec. 4-8, 2018; San Antonio.)

### 1.8 Rationale to study the effects of immunotherapy on disseminated tumor cells in the bone marrow

Disseminated tumor cells (DTCs) are tumor cells that escape the environment of a primary breast tumor, and seed distant niches, such as bone marrow (BM), where they can serve as a source for future, metastatic spread [57]. DTCs can be detected in the BM of up to 40% of patients with early stage BC without any clinical signs of metastasis. The presence of DTCs is associated with an increased rate of distant recurrence in breast cancer patients [58]. Interestingly, the molecular phenotype of DTCs, particularly with regard to targeted therapeutic sensitivities, is often distinct from the primary breast tumor from which they originate [59]. Tumor cells evoke a number of molecular mechanisms to avoid immune recognition and destruction, and these pathways may be critical for establishing DTC dormancy in the BM of breast cancer patients [60]. The molecular characterization of DTCs based upon specific gene mutations or gene expression profiles is feasible. Multi-marker, gene expression-based panels can provide a sensitive, specific, and technically streamlined approach to the detection and classification of BM DTCs [61-63]. Our research team (Aft, Watson) has developed methods to enrich, detect, and classify DTCs in breast cancer patients correlating the presence of DTCs with prognosis and response to anti-cancer

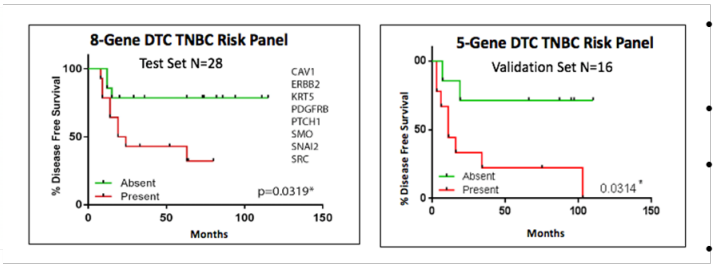
treatments. The correlative work in this trial is heavily focused on exploring the biological and immunological basis for DTC dormancy, to understand the molecular heterogeneity of DTCs and to investigate the effects of immunotherapy on DTCs and their microenvironment.

We have defined an 8-gene BM DTC expression panel, assayed prior to neoadjuvant therapy, that is associated with incomplete response to neoadjuvant chemotherapy and early distant metastasis in 'triple negative' (TN) breast cancer patients.

**8-gene BM DTC marker panel vs. pCR in treatment naïve TN Breast Cancer (n=28)**

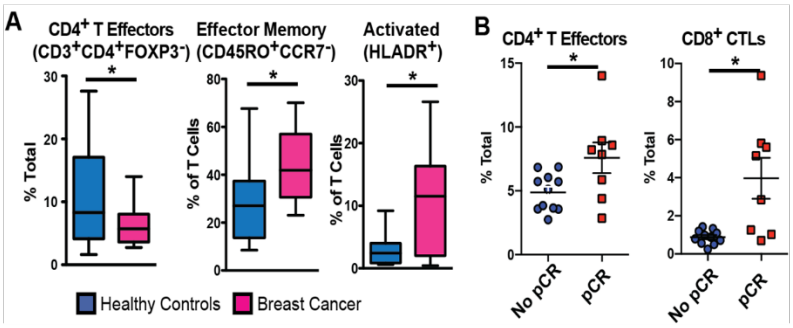
| | pCR | RD |
|---|---|---|
| Gene panel + | 0 | 14 |
| Gene panel - | 6 | 8 |

**P= 0.016** (Fisher's Exact)




- Identified by whole transcriptome analysis of healthy vs. BRCA BM samples.
- 46 gene transcripts validated by nCounter and qPCR platforms.
- 8-gene panel optimized for TN patients using sensitive and quantitative DDPCR.
- Biased for "actionable" targets.

- DTCs persist in the BM of breast cancer patients, even after conventional chemotherapy.
- The BM Immune microenvironment differs in patients with BC and by treatment response.




**T cells changes in the bone marrow of BC patients.**
(A) BC patients BM samples taken prior to any therapy, were analyzed by flow cytometry and the frequency of T cell populations is depicted (n=20).
(B) Relative numbers of BM T cells stratified by patients who achieved pathologic complete responses (pCR).

Meyer M et al. Nature Communications 2018

- **Monitoring changes in the BM immune microenvironment will facilitate a better understanding of DTC 'latency' and predict response to immunotherapy modalities for preventing future metastatic disease.**

## 1.9 Rationale for Amendment 7 (Removal of Cabiralizumab)

After completion of the 12-patient safety run-in and with the activation of Amendment 7, this study has been changed to a single-arm, non-randomized study because cabiralizumab has an expiry date prior to the planned completion of enrollment of the two-arm randomized trial. The initial signal from the safety run-in of the non-cabiralizumab trial arm that includes carboplatin, paclitaxel, and nivolumab (Arm A) demonstrated early evidence of safety and preliminary evidence of efficacy that warranted further evaluation with additional patients.

Notably, in July 2021, neoadjuvant chemotherapy in combination with pembrolizumab was approved by the FDA based on KEYNOTE-522 (NCT03036488), a randomized, double-blind, placebo-controlled trial of 1174 patients. The regimen includes four chemotherapy

drugs (carboplatin, paclitaxel, cyclophosphamide, and an anthracycline) combined with both neoadjuvant and adjuvant pembrolizumab. This study demonstrated an improved pathological complete response rate and event-free survival of chemotherapy regimen with pembrolizumab compared to the control arm. However, there are ongoing questions regarding chemotherapy and immune-related toxicities of the regimen, the necessity of an anthracycline, and the need for adjuvant immune checkpoint inhibition for all patients. The median age of the patients included in the trial was less than 50 with nearly 90% of patients less than 65 years of age. Therefore, alternative neoadjuvant treatment options that include both chemotherapy and immune checkpoint inhibition are needed for patients that have lower toxicity and better tolerance.

In this single-arm study, all patients enrolled will receive 12 weeks of neoadjuvant carboplatin, paclitaxel, and nivolumab. Adjuvant therapy is per investigator's choice. For patients who have a pathological complete response after neoadjuvant therapy, anthracycline therapy can likely be avoided, and adjuvant immune checkpoint inhibition can be considered. In contrast, for patients without a pathological complete response, adjuvant anthracycline with cyclophosphamide and immune checkpoint inhibition can be given with similar therapies split between neoadjuvant and adjuvant therapy as given in KEYNOTE-522. The current single-arm study, which includes robust biomarker analysis including tissue, peripheral blood, and bone marrow analyses, may permit a precision medicine approach by allowing the utilization of a de-escalated regimen for some patients, while still permitting anthracycline therapy for other patients who require additional therapy after surgery. Both chemotherapy and immune-related adverse events are anticipated to be lower than KEYNOTE-522 based on the shorter duration of therapy and fewer drugs incorporated into the treatment regimen.

## 2.0 OBJECTIVES AND ENDPOINTS

| **Objectives** | **Endpoints** | **Justification for Endpoints** |
|---|---|---|
| **Primary** | | |
| Safety Lead-In: To investigate if the combination of neoadjuvant chemotherapy with nivolumab and cabiralizumab is safe in patients with TNBC. | Toxicity by CTCAE v 5.0. | The study includes a safety lead-in part that will assess safety of the combination of nivolumab +/- cabiralizumab with NAC. |
| To compare on-treatment TAMs and TILs against their baseline levels in patients with newly diagnosed stage II/III TNBC treated with neoadjuvant nivolumab + chemotherapy. | Percent change of on-treatment TAMs from baseline and percent change of on-treatment TILs from baseline (stromal TIL score is defined as the percentage of tumor stroma area that was | TILs, mainly the CD8 +T cells, have been identified and validated as a predictive and prognostic biomarker of long-term survival in TNBC treated with neoadjuvant chemotherapy. In |

| | | |
|---|---|---|
| | occupied by mononuclear inflammatory cells). | metastatic TNBC patients treated with a PD-L1 inhibitor, response rate and overall survival significantly correlated with the level of TILs |
| **Secondary** | | |
| To estimate the pathological complete response (pCR) rate in patients with newly diagnosed stage II/III TNBC treated with neoadjuvant nivolumab + chemotherapy. | pCR rate | pCR defined as complete absence of disease in the breast and lymph nodes-after NAC is associated with improved outcomes in TNBC. Therefore, pCR has been used as a primary endpoint in most neoadjuvant trials in TNBC. It is important to acknowledge that even though there is a clear correlation between pCR with chemotherapy and long-term outcomes in TNBC, there is uncertainty on how clear the correlation is with immune therapy combinations. We will also evaluate residual cancer burden (RCB) status in all patients. |
| To estimate the grade 3 or higher treatment-related adverse event rate. | Grade 3 or higher treatment-related AE rate. | Observed grade 3+ toxicity events in prior studies are high and can lead to impaired quality of life, long-term toxicity, treatment delays and, at times, early treatment discontinuation. |
| To compare the percent change of TAMs and TILs between who achieve a pCR after treatment with neoadjuvant nivolumab and chemotherapy versus those who do not. | TILs and TAMs percentage will be measured at baseline and after initiation of therapy. | TILs, mainly the CD8 +T cells, have been identified and validated as a predictive and prognostic biomarker of long-term survival in TNBC treated with neoadjuvant chemotherapy. In metastatic TNBC patients |

| | | |
|---|---|---|
| | | treated with a PD-L1 inhibitor, response rate and overall survival significantly correlated with the level of TILs |
| To determine recurrence-free survival (RFS) | Recurrence-free survival (RFS) defined from time of surgery to the earliest time of recurrence, time to development of a second cancer, or time to death from any cause. | RFS is a widely accepted end point to assess clinical benefit of a new treatment. In this study, we will investigate the effect of adding a novel immunotherapy combination to NAC in TNBC patients. |
| **Exploratory** | | |
| To evaluate disseminated tumor cell (DTC) gene signature elimination in the bone marrow after neoadjuvant treatment and correlation with pCR and prognosis. | | |
| To evaluate potential biomarkers of response to NAC + nivolumab +/- combination with cabiralizumab in patients with newly diagnosed TNBC. Potential biomarkers include baseline TAMs and/or TILs percentage, baseline PD-L1 expression in the tumor and tumor infiltrating immune cells, CSF-1R+. These biomarkers will be correlated with pathologic complete response. | | |
| To compare the difference in the immune cell infiltration and cytokine expression in the biopsied tumors of patients with TNBC before and after treatment with the combination of NAC plus nivolumab. | | |
| To correlate changes in the immune infiltrate with clinical responses to treatment with the combination of NAC plus nivolumab and clinical outcomes (pCR, RFS) following treatment. | | |
| To compare the difference in ctDNA response in patients who achieve pCR vs. patients who do not achieve pCR. | | |

# 3.0 STUDY POPULATION

## 3.1 Inclusion Criteria

1. Histologically or cytologically confirmed newly diagnosed ER-/HER2- breast cancer. ER and PR < Allred score of 3 or < 1% positive staining cells in the invasive component of the tumor. HER2 negative by FISH or IHC staining 0 or 1+ according to ASCO/CAP guidelines.

2. Clinical stage II or III (by AJCC 8$^{th}$ edition – at least T2, any N, M0 or if N+ then any T) breast cancer eligible for neoadjuvant chemotherapy with complete surgical excision of the breast cancer after neoadjuvant therapy as the treatment goal.

3. Tumor size at least 2 cm in one dimension by clinical or radiographic exam (WHO criteria). Patients with histologically confirmed or clinically palpable lymph nodes may be enrolled regardless of tumor size. A palpable mass is not required as long as the mass is at least 2 cm in one dimension by radiographic exam. 2D measurements should be completed during screening if available.

4. No prior therapy for this disease

5. At least 18 years of age.

6. ECOG performance status ≤ 1 (see Appendix A)

7. Normal bone marrow and organ function as defined below:
   a. Leukocytes ≥ 2,000/mcL (stable off any growth factor within 4 weeks of first study treatment administration)
   b. Absolute neutrophil count ≥ 1,500/mcL (stable off any growth factor within 4 weeks of first study treatment administration)
   c. Platelets ≥ 100,000/mcL (stable off any growth factor within 4 weeks of first study treatment administration)
   d. Hemoglobin ≥8.5 g/dl (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)
   e. Total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except participants with Gilbert's Syndrome who must have normal direct bilirubin)
   f. AST(SGOT)/ALT(SGPT) ≤ 2.0 x IULN
   g. Alkaline phosphatase ≤2.5 x ULN
   h. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 40 mL/min by Cockcroft-Gault
   i. Albumin ≥ 3 g/dL
   j. INR and aPTT ≤1.5 x IULN (This applies only to patients who **do not** receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation, such as low-molecular-weight heparin or warfarin, should be on a stable dose).

8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment.

9. Women must not be breastfeeding.

10. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) and for a total of 5 months post-treatment completion.

11. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

12. Consent for fresh pre-treatment, on-treatment, biopsy samples at acceptable clinical risk, as judged by the investigator.

13. Participants must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing

### 3.2 Exclusion Criteria

1. Prior treatment with immunotherapy for cancer

2. Known metastatic disease

3. Known invasive cancer in contralateral breast

4. Patients with a previous history of non-breast malignancy are eligible only if they meet the following criteria for a cancer survivor:
   - Has undergone potentially curative therapy for all prior malignancies AND
   - Has been considered disease-free for at least 1 year (with the exception of basal cell or squamous cell carcinoma of the skin or carcinoma-in-situ of the cervix).

5. Currently receiving any other investigational agents.

6. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to paclitaxel, carboplatin, nivolumab, or other agents used in the study. Patients who have received multiple blood transfusions.

7. Evidence of uncontrolled ongoing or active infection, requiring parenteral anti-bacterial, anti-viral, or anti-fungal therapy $\leq$ 7 days prior to administration of study treatment. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

8. Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

9. History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

   - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
   - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.

- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
  - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

10. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan.

11. Uncontrolled or significant cardiovascular disease

12. History of any chronic hepatitis as evidenced by the following:
    - i) Positive test for hepatitis B surface antigen
    - ii) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR]).

13. Positive test for latent tuberculosis (TB) at screening (e.g. T-SPOT or Quantiferon test) or evidence of active TB.

14. Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study with the exception of the planned breast cancer surgery that is part of the trial design. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

15. Any uncontrolled medical condition which, in the opinion of the Investigator, would pose a risk to participant safety or interfere with study participation or interpretation of individual participant results.

16. Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.
    - Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
    - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

The use of replacement doses of prednisone or other corticosteroid for adrenocortical insufficiency is allowed

- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.

17. Evidence of coagulopathy or bleeding diathesis.

18. Ascites needing paracentesis or medical management.

19. Patients positive for human immunodeficiency virus (HIV) are NOT excluded from this study, but HIV-positive patients must have:
    - A stable regimen of highly active anti-retroviral therapy (HAART)
    - No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
    - A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests

### 3.3 Inclusion of Women and Minorities

Men and women and members of all races and ethnic groups are eligible for this trial.

## 4.0 REGISTRATION PROCEDURES

**Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.**

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

### 4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

## 4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

## 4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

## 4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

## 4.5 Randomization

Patients will be randomized at a 1:1 ratio between Arm A (neoadjuvant chemotherapy + nivolumab) and Arm B (neoadjuvant chemotherapy + nivolumab + cabiralizumab) and will be stratified by clinical stage (stage II vs stage III). A stratified block randomization will be used with varying block size of 2 to 4. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.

After the conclusion of the safety run-in and with the activation of Amendment 7, randomization is discontinued. All patients enrolled thereafter will be treated on Arm A.

## 4.6 Strategies for Recruitment and Retention

Triple negative breast cancer (TNBC) lacks specific therapeutic targets. Therefore, treatment options are limited to chemotherapy in the neoadjuvant setting. If patients relapse after NAC and definitive surgery, outcomes are typically poor. Of importance, our institution is becoming a national leader in developing personalized vaccines and other novel approaches to treat breast cancer with many patients being referred to our institution for treatment. Based on the current trend, we estimate 4 new patients per month with TNBC to be treated at our institution at the time of study opening.

We believe that this trial will have excellent patient accrual. The primary source of patients who are eligible for this study is via the surgical and medical oncologists specializing in breast cancer treatments. Dr. Rebecca Aft from the surgical oncology team is a collaborator and sub-investigator of this study and is very supportive of this clinical trial. The fact that

the current treatment strategy for TNBC at this institution is similar to this study protocol should lend further reassurance that this study ought to have excellent patient accrual.

With the current rate of TNBC patients presenting at our institution, we anticipate approximately 60 patients per year who will be treated at our institution. A conservative estimate is that 50% of these patients will consent to participate in this study. This yields an estimated accrual of 30 patients per year. We anticipate that we will enroll 51 adult patients (>18 years of age) of all genders, races, and ethnicities. We anticipate that 60 patients will be screened to reach target enrollment. We anticipate that we will accrue approximately 2 patients per month, therefore completing accrual in approximately 2 years. Patients will be accrued from the outpatient clinics and inpatient hospitals of one U.S. site. Potential participants will be identified by our multidisciplinary team physicians and discussed in tumor board.

# 5.0 TREATMENT PLAN

## 5.1 Premedication Administration

Premedications in order to avoid the occurrence of sever hypersensitivity reactions to paclitaxel and carboplatin will be administered per institutional standard.

See Section 10.2 for instructions on data collection on concomitant medication.

## 5.2 Study Intervention Description

During the safety run-in, consenting and eligible patients will be randomized to Arm A or Arm B. After the conclusion of the safety run-in and with the activation of Amendment 7, randomization is discontinued and all patients will be enrolled to Arm A.

Arm A is paclitaxel + carboplatin + nivolumab. Arm B is paclitaxel + carboplatin + nivolumab + cabiralizumab. Paclitaxel and carboplatin are chemotherapies approved for administration to patients with breast cancer. Nivolumab is an anti-PD-1 monoclonal antibody which works as a checkpoint inhibitor. It is approved for several indications, including melanoma, metastatic non-small cell and small-cell lung cancers, advanced renal cell carcinoma, relapsed classical Hodgkin lymphoma, recurrent or metastatic head and neck cancer, advanced or metastatic urothelial carcinoma, metastatic colorectal cancer, and hepatocellular cancer, but is not approved for breast cancer and is therefore considered investigational in the context of this study. Cabiralizumab is an investigational agent and is not approved by the FDA.

## 5.3 Study Intervention Administration

All patients enrolled to this study must receive neoadjuvant paclitaxel + carboplatin for their neoadjuvant chemotherapy. Paclitaxel will be given intravenously at a dose of 80 mg/m2 IV over 1 hour (+/- 15 min) on a weekly basis for 12 weeks (Weeks 1, 2, 3, 4, 5, 6,

7, 8, 9, 10, 11, and 12). Carboplatin will be given intravenously at a dose of AUC 5 IV over 30 min (+/- 10 min) every 3 weeks for 12 weeks (Weeks 1, 4, 7, and 10).

All patients enrolled to this study will also receive nivolumab as part of their neoadjuvant therapy. Nivolumab will be given intravenously at a dose of 240 mg over 30 minutes (+/- 5 min) every 2 weeks for 12 weeks (Weeks 1, 3, 5, 7, 9, and 11). In patients randomized to Arm A, nivolumab will be administered first, starting 30 min (+/- 5 min) after treatment start time), followed by paclitaxel starting 60 min (+/- 15 min) after treatment start time, followed by carboplatin starting 2 hours (+/- 15 min) after treatment start time.

Patients randomized to Arm B will also receive cabiralizumab as part of their neoadjuvant therapy. Cabiralizumab will be given intravenously at a dose of 4 mg/kg over 30 minutes every 2 weeks for 12 weeks (Weeks 1, 3, 5, 7, 9, and 11). In patients randomized to Arm B, nivolumab will be administered first, starting 30 min (+/- 5 min) after treatment start time), followed by cabiralizumab starting 60 min (+/- 15 min) after treatment start time, followed by paclitaxel starting 90 min (+/- 15 min) after treatment start time, followed by carboplatin starting 2.5 hours (+/- 15 min) after treatment start time.

Definitive surgery will be performed 4 to 8 weeks after the end of neoadjuvant treatment per treating surgeon discretion. Adjuvant therapy following definitive surgery will be at the discretion of the treating oncologist.

The first six patients randomized to each arm will be part of a safety run-in. The allocation to an arm will pause after enrollment of the sixth patient to that arm until all six patients in that arm have completed all 12 weeks of treatment and have passed the toxicity monitoring period (4 weeks after last infusion of nivolumab and/or cabiralizumab or surgery whichever occurs first). Refer to Section 13.6 for early stopping rules.

## 5.4 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment, day of surgery, or death, whichever comes first.

Patients are considered evaluable for the primary objective if they satisfy eligibility criteria, have received at least 2 doses of the total immunotherapeutic drug dosage, and have valid baseline and on-treatment TAMs and TILs measurements for a percent change evaluation of TAMs and TILs. Patients who cannot have the on-treatment biopsy may continue to receive treatment on study but must be replaced.

In order to be evaluable for pCR and RFS, patients must meet the eligibility requirements and have been assessed for pCR (undergone surgery or have documented disease progression prior to surgery).

## 5.5 Concomitant Therapy and Supportive Care Guidelines

See Section 10.2 for instructions regarding collection of concomitant medications.

Growth factor support (GFS) is permitted when patients are on study per discretion of the treating physician. GFS is not allowed during screening due to lab requirements.

### 5.5.1 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, urticaria, angioedema, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

Remain at bedside and monitor subject until recovery from symptoms

**For Grade 1 symptoms:** (Mild reaction; infusion interruption not indicated; intervention not indicated)

Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

**For Grade 2 symptoms:** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours, and no further nivolumab will be administered at that visit.)

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered

as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

**For Grade 3 or Grade 4 symptoms:** (Severe reaction),

> **Grade 3 symptoms:** prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]).
>
> **Grade 4 symptoms:** (life threatening; pressor or ventilatory support indicated).

Nivolumab will be permanently discontinued.

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

### 5.5.2 Restricted Concomitant Therapies

The following therapies are restricted:

- Concomitant use of statins while on study. However, a participant using statins for over 3 months prior to study drug administration and in stable status without CK rise may be permitted to enroll.
- Receipt of a live/attenuated vaccine within 30 days of first treatment. The inactivated seasonal influenza vaccine can be given to participants before treatment and while on therapy without restriction.

## 5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the first dose of study treatment.

Heterosexually active patients are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 5 months following the last dose of any study treatment.

If a patient is suspected to be pregnant, all study treatment should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a patient becomes pregnant during therapy or within 5 months after the last dose of any study treatment, the investigator must be notified in order to facilitate outcome follow-up.

## 5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 12 weeks or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent

- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

### 5.8 Duration of Follow-up

Patients will be followed for 3 years after discontinuation of treatment or until death, whichever occurs first. Follow-up will be at 6 months and one year post-surgery and on an annual basis thereafter for an additional 2 years (3 years total). Patients who come off study treatment prior to surgery will be followed for 100 days for adverse events and will continue to be followed for survival only. Patients unable to complete all of the prescribed treatments due to an adverse event will be followed until resolution or stabilization of the adverse event and after will enter the follow up period as above.

### 5.9 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 6.0 DOSE DELAYS/DOSE MODIFICATIONS

Recommended dose holds and modifications for the standard of care neoadjuvant chemotherapy are described in Section 6.1, but additional modifications may be made at the discretion of the treating physician.

If the AE requiring hold and/or discontinuation was due to one of the study drugs, the non-offending drug(s) may be continued, at the discretion of the treating physician and PI.

Dose holds and modifications for paclitaxel, carboplatin, nivolumab and cabiralizumab (for the safety lead-in patients; cabiralizumab is not given to any patients enrolled after the safety lead-in) are specified in Sections 6.2 and 6.3. Other holds and modifications may be made at the discretion of the treating physician and PI.

Nivolumab and cabiralizumab will be held when paclitaxel and/or carboplatin are held. If cabiralizumab is held, nivolumab and paclitaxel and/or carboplatin can continue. If there is a need to discontinue chemotherapy (such as due to severe hypersensitivity reaction), patients should continue to surgery.

### 6.1 Dosing Adjustments for Standard of Care Chemotherapy

**Paclitaxel Dose Levels**

| Level | Dose |
|---|---|
| Starting Dose | 80 mg/m$^2$ |
| Dose Level -1 | 65 mg/m$^2$ |
| Dose Level -2 | 50 mg/m$^2$ |
| Dose Level -3 | Discontinue |

**Carboplatin Dose Levels**

| Level | Dose |
|---|---|
| Starting Dose | AUC 5 |
| Dose Level -1 | AUC 4 |
| Dose Level -2 | AUC 3 |
| Dose Level -3 | Discontinue |

Dose modifications must be based on the AE requiring the greatest modification. Chemotherapy doses that have been reduced may not be escalated. Chemotherapy should be held for at least 1 week until any chemotherapy-related AE requiring dose modification returns to ≤ grade 1 unless indicated otherwise below. If recovery to ≤ grade 1 (or to other level specified) has not occurred after 3 weeks of delay, therapy must be discontinued.

| **CTCAE v 5.0 grade** | **Modifications for AEs that occurred between treatments but did NOT require a delay in treatment (for paclitaxel) or resolve prior to the next treatment cycle (for carboplatin); treatment may NOT proceed until clinically significant AEs are ≤ grade 1 (except neutrophils, which must be ≥ 1000/mm3 and bilirubin, which must be ≤ the baseline grade) (in between treatments)** | **Day of treatment: Modifications for AEs that require a delay in the next treatment; hold and check weekly, and resume treatment when toxicity is ≤ grade 1 (with the exception of neutrophils and bilirubin); if toxicity has not resolved to ≤ grade 1 after 3 weeks of delay, DISCONTINUE PACLITAXEL AND CARBOPLATIN** |
|---|---|---|
| Neutrophil count decreased | | |

| | | |
|---|---|---|
| Grade 2 | Maintain doses | Maintain dose of paclitaxel.<br>2nd occurrence – consider adding G-CSF) |
| Grades 3, 4 | | • Hold paclitaxel until ANC ≥ 1000/mm3. Maintain dose of paclitaxel and add G-CSF (if already receiving G-CSF, reduce paclitaxel by one dose level).<br>• Hold carboplatin until ANC ≥ 1000/mm3.<br>• If recovery takes 1 week, maintain dose of carboplatin and add G-CSF.<br>• If recovery takes 2 weeks, reduce carboplatin by one dose level and add G-CSF.<br>• If recovery takes 3 weeks, discontinue carboplatin.<br>• If already receiving G-CSF and recovery takes 1 week, reduce carboplatin by one dose level.<br>• If already receiving G-CSF and recovery takes > 1 week, discontinue carboplatin.<br>• For grade 4 toxicity. Resuming treatment after discussion with the research team |
| Platelet count decreased | | |
| Grades 2, 3 | Maintain doses | • Hold both until platelets ≥ 75,000/mm3.<br>• If recovery takes 1 week, maintain dose of paclitaxel and reduce carboplatin by one dose level.<br>• If recovery takes > 1 week, reduce paclitaxel by one dose level and reduce carboplatin by two dose levels or discontinue. |
| Grade 4 | Discontinue treatment | Discontinue treatment |
| Anemia | | |
| Grade 3, 4 | Hold until > or equal to grade 2. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. Use of erythropoiesis-stimulating agents is prohibited. | |

| | | |
|---|---|---|
| | For grade 4 toxicity. Resuming treatment after discussion with the research team | |
| Diarrhea (if related to chemotherapy) | | |
| Grade 2<br><br>(despite full anti-diarrhea therapy) | Maintain doses | Maintain paclitaxel dose or reduce by one dose level. Reduce carboplatin by one dose level.<br>(Consider stool leukocytes and infectious workup). |
| Grade 3 (despite full anti-diarrhea therapy) | Reduce both by one dose level | |
| Grade 4 | Hold, initiate workup. If not due to autoimmune component – treat as per standard of care and resume when equal to or better than grade 3. Reduce paclitaxel by one dose level or discontinue. Reduce carboplatin by two dose levels or discontinue. Resuming treatment after discussion with the research team | |
| Mucositis – oral (if related to chemotherapy) | | |
| Grade 2 | Maintain doses | Maintain paclitaxel dose or reduce by one dose level. Reduce carboplatin by one dose level. |
| Grade 3 | Hold until equal to or better than grade 2. Reduce both by one dose level | |
| Grade 4 | Hold until equal to or better than grade 2. Reduce paclitaxel by one dose level or discontinue. Reduce carboplatin by two dose levels or discontinue. Resuming treatment after discussion with the research team | |
| Vomiting (if related to chemotherapy and despite antiemetics) | | |
| Grade 2 | Maintain doses or reduce both by one dose level (preferred modification is to add anti-nausea medications to pre-treatment) | |
| Grades 3, 4 | Reduce both by one dose level or discontinue<br>For grade 4 toxicity. Resuming treatment after discussion with the research team | Hold until equal to or better than grade 2. Modify pre-treatment anti-nausea medications as per standard of care. Reduce paclitaxel by one dose level or discontinue. Reduce carboplatin by two dose levels or discontinue.<br>For grade 4 toxicity. Resuming treatment after discussion with the research team |
| Elevation in AST/alkaline phosphatase and/or bilirubin | | |
| Grade 2 | Maintain doses or reduce both by one dose level. | Hold until bilirubin returns to the baseline grade and AST and alk phos have returned to ≤ grade 1, consider reducing either paclitaxel and/or carboplatin by one dose level |
| Grade 3 | Consider reducing paclitaxel by one dose level or discontinue. | Hold until bilirubin returns to the baseline grade and AST and alk phos have returned to ≤ grade 1, then |

| | | |
|---|---|---|
| | Reducing carboplatin by one dose level or discontinue. | reduce paclitaxel by one dose level or discontinue and reduce carboplatin by two dose levels or discontinue. |
| Grade 4 | Discontinue both. | |
| Infection or febrile neutropenia | | |
| Grade 2 | Consider hold if clinically indicated. Maintain doses and add G-CSF prophylaxis for subsequent chemotherapy cycles if neutropenia was present. (If grade 2 criteria for infection include topical antibiotics or other local treatment, use of G-CSF is at the investigator's discretion.) | |
| Grade 3 | Hold until resolves to grade 2 or better. Maintain doses and add G-CSF prophylaxis for subsequent chemotherapy cycles. If receiving prophylactic G-CSF, reduce both by one dose level. | |
| Grade 4 | Hold until resolves to grade 2 or better. Maintain doses or reduce both by one dose level and add G-CSF prophylaxis for subsequent chemotherapy cycles. If receiving prophylactic G-CSF, reduce both by one dose level or discontinue. | |
| Creatinine increased | | |
| Grades 2, 3 | Hold until creatinine ≤ grade 1 or less than or equal 1.5 X baseline. Resume paclitaxel at same dose level.<br>Hold carboplatin until serum creatinine is ≤ grade 1 equal 1.5 X baseline AND measured or calculated creatinine clearance is ≥ 30 mL/min. If creatinine clearance is > 50 mL/min, maintain dose of carboplatin. If creatinine clearance is 30-50 mL/min, reduce carboplatin by one dose level. If measured or calculated creatinine clearance is < 30 mL/min but all other non-renal function AEs have resolved to ≤ grade 1 on the scheduled Day 1, carboplatin must be held. If measured or calculated creatinine clearance subsequently improves to ≥ 30 mL/min, carboplatin may be resumed. The missed carboplatin dose will not be made up. | |
| Grade 4 | Hold until creatinine ≤ grade 1 or less than or equal 1.5 X baseline. Resuming treatment after discussion with the research team. Maintain paclitaxel. Discontinue carboplatin. | |
| Other clinically significant AEs related to chemotherapy (at the discretion of the investigator)*** for CK elevations please refer to CK table | | |
| Grade 2 | Hold until grade 1 or better. Maintain doses or reduce both by one dose level | |
| Grade 3 | Hold until grade 1 or better. Reduce both by one dose level | |
| Grade 4 | Hold until grade 1 or better. Reduce paclitaxel by one dose level or discontinue. Reduce carboplatin by two dose levels or discontinue. Resuming treatment after discussion with the research team and safety committee. | |

**Treatment management for paclitaxel-related neuropathy**

| **Nervous System Disorders (Paresthesias, peripheral sensory neuropathy)** | **1-7 days duration** | **Persistent for > 7 days OR caused the next treatment to be delayed** |
|---|---|---|

| | | |
|---|---|---|
| Grade 1 | Maintain dose | |
| Grade 2 | Maintain dose (must be resolved to ≤ grade 1 on the next treatment day) | Continue treatment. Consider reducing by one dose level treatment with dose modification for paclitaxel. Stop therapy as clinically indicated. |
| Grade 3 | First episode:<br>Reduce by one dose level (must be resolved to ≤ grade 1 on the next treatment day)<br>Second episode:<br>Discontinue paclitaxel | Discontinue paclitaxel |
| Grade 4 | Discontinue paclitaxel | |

**Treatment management for paclitaxel-related musculoskeletal pain**

| **Musculoskeletal and Connective Tissue Disorders (Arthralgia, myalgia)** | **1-7 days duration** | **Persistent for > 7 days OR caused the next treatment to be delayed** |
|---|---|---|
| Grade 1 | Maintain dose | |
| Grade 2 | Maintain dose | Maintain dose or reduce by one dose level (hold paclitaxel and carboplatin for persistent grade 2 musculoskeletal pain (despite opioid therapy); Persistent pain – consider workup for myositis. When ≤ grade 1, resume treatment with dose modification for paclitaxel but no dose modification for carboplatin. If grade 2 toxicity persists after 3 weeks of delay, discontinue all chemotherapy) |
| Grade 3 (despite opioid therapy) | First episode:<br>Reduce by one dose level<br>Second episode:<br>Reduce by 1 dose level or Consider discontinuing paclitaxel | First episode<br>Reduce by one dose level or discontinue (hold paclitaxel and carboplatin for persistent grade 3 musculoskeletal pain; when ≤ grade 1, resume treatment with dose modification for paclitaxel but no dose modification for carboplatin. If grade 3 toxicity persists after 3 weeks of delay, discontinue all chemotherapy)<br>Second episode<br>Discontinue paclitaxel |

*Note: these instructions only apply to patients with musculoskeletal pain not controlled by analgesics. Use of narcotics and NSAIDs is encouraged to maintain the paclitaxel dose if possible.*

<u>Other treatment management instructions</u>

- If a paclitaxel-related hypersensitivity reaction occurs despite premedication, treatment as medically indicated will be instituted. For ≤ grade 3 allergic reaction or grade 3 anaphylaxis, continuation of paclitaxel is at the investigator's discretion. Following a grade 4 allergic reaction or grade 4 anaphylaxis, paclitaxel must be permanently discontinued. Can be changed to nab-paclitaxel as per institutional standards.
- Carboplatin must be permanently discontinued if a grade 3 or 4 hypersensitivity reaction occurs that the investigator attributes to carboplatin.
- Paclitaxel and carboplatin must be completed within 18 weeks. Any of the 12 paclitaxel doses or 4 carboplatin doses remaining after 18 weeks following the first paclitaxel and carboplatin doses should not be administered.

### 6.2 Dosing Adjustments for Nivolumab

Please refer to Appendix B for toxicity management algorithms which include specific treatment guidelines. However, there are algorithms in this section that may be different from Appendix B. In these cases, please follow the protocol specific dose modification guidelines in this section unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. These treatment guidelines apply to adverse events that are attributed to nivolumab per treating physician. Laboratory abnormalities or adverse events that per treating physician are related to chemotherapy and/or cabiralizumab do not require modification in nivolumab dosing or schedule. Consultation with the study PI is recommended.

Generally, we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

| Cardiac * | Management/Next Dose for Nivolumab Cardiac Toxicities |
|---|---|
| Less than grade 2 | Hold all treatments pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below. |
| Grade ≥2 | Hold all treatements.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if it was asymptomatic troponin raise and there is a return to baseline and myocarditis is excluded or considered unlikely. Other asymptomatic abnormalities can also be considered for resumption of therapy after consultation with research team. |

| Cardiac * | Management/Next Dose for Nivolumab Cardiac Toxicities |
|---|---|
| Grade ≥2 with confirmed myocarditis | Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone<br>Add ATG or tacrolimus if no improvement. Off protocol treatment. |
| **Including CHF, LV systolic dysfunction, Myocarditis, , and troponin **Patients with evidence of myositis without myocarditis may be treated according as "other event"*<br>Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended. | |

| **ALL OTHER EVENTS NOT OTHERWISE NOTED** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | No change in dose |
| Grade 2 | Hold until ≤ Grade 1 OR baseline (exceptions as noted below) |
| Grade 3 | Off protocol therapy (exceptions as noted below) |
| Grade 4 | Off protocol therapy |
| Recommended management: As clinically indicated | |

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment
- Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

| **Skin Rash and Oral Lesions** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | No change in dose * |
| Grade 2 | Hold* until ≤ Grade 1 . Resume at same dose. |
| Grade 3 | Hold* until ≤ Grade 1. Resume at investigator discretion |
| Grade 4 | Off protocol therapy |
| *Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering. | |

| |
|---|
| Recommended management: AE management guidelines |

| **Liver Function AST, ALT, and Bilirubin elevation** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Consider holding if rapid raise and no alternative explanation likely until ULN or baseline. Resume at same dose. |
| Grade 2 | Hold until grade 1 (ULN – 3x ULN) or baseline and resume at same dose at investigator discretion. |
| Grade 3 | Hold until grade 1 or baseline. Resume therapy at investigator discretion with return to grade 1 or baseline within 7 days without steroids. If determined it was due to nivolumab and AST/ALT were > 8 X ULN and/or bilirubin was > 3 X ULN permanently discontinue. If persistent or steroids are required, off protocol therapy. |
| Grade 4 | Off protocol therapy |
| Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended.<br>LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.<br>Please note: grades for liver function follow ULN rather than multiples of baseline. | |
| Recommended management: see Hepatic AE management algorithm | |

| **Diarrhea/ Colitis** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | May continue – close monitoring of symptoms recommended. Consider workup for infectious causes. |
| Grade 2 | Hold until baseline. Resume at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. |
| Grade 3 | Resume treatment at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. If persistent or steroids are required, may consider resuming if symptoms resolve and steroids equivalent to < or equal to 10 mg of prednisone a day. |
| Grade 4 | Off protocol therapy |
| See GI AE Algorithm for management of symptomatic colitis.<br>Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated.<br>Patients who require systemic steroids may consider resuming if all symptoms have resolved after steroid taper.<br>Please evaluate pituitary function prior to starting steroids if possible without compromising acute care.<br>Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD. | |
| Recommended management: see GI AE management Algorithm | |

| **Pancreatitis Amylase/Lipase** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Continue treatment if asymptomatic at investigator discretion |
| Grade 2 | Continue treatment if asymptomatic at investigator discretion. If symptomatic, resume treatment when resolved. |
| Grade 3 | Continue treatment if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (if grade 3 symptomatic pancreatitis is confirmed – stop nivolumab permanently) before resuming treatment. Workup for diabetes indicated. |
| Grade 4 | Hold until grade 2. Resume if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 3 or 4 symptomatic pancreatitis stop nivolumab permanently. |
| Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetes ketoacidosis. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated.<br>For treatment management of symptomatic pancreatitis please follow the Hepatic AE Management Algorithm | |

| **Pneumonitis** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Hold dose pending evaluation, consider pulmonary consult. Continue treatment as clinically indicated. |
| Grade 2 | Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis as the cause of the pneumonitis. Stop nivolumab permanently if prolonged (> 4 weeks) steroids are required. |
| Grade 3 | Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis as the cause of the pneumonitis. If cause is likely autoimmune pneumonitis stop nivolumab permanently. |
| Grade 4 | Off protocol therapy |
| Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. All patients should have COVID testing. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients. | |
| Recommended management: See Pulmonary AE Management Algorithm | |

| **Fatigue** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 2 | No change in dose |
| Grade 3 | Hold until ≤ Grade 2. Resume treatment at discretion of investigator. |
| Grade 4 | Nivolumab permanently discontinued |
| Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation | |

| **Neurologic events** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline. . |
| Grade 2 | Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Nivolumab to be permanently discontinued if prolonged (>4 weeks) treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy) |
| Grade 3 | Off protocol therapy |
| Grade 4 | Off protocol therapy |
| Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study. | |
| Recommended management: See Neurologic AE Management Algorithm | |

| **Endocrine Hypophysitis Adrenal Insufficiency** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | *Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement. |
| Grade 2 | Hold pending evaluation and may resume while on replacement hormone regimen. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment with initiation of replacement therapy. If treated with steroids patients must be stable off steroids prior to resumption of therapy. Resume treatment. |
| Grade 3 | Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids. |

| **Endocrine Hypophysitis Adrenal Insufficiency** | **Management/Next Dose for Nivolumab** |
|---|---|
| | Resume treatment. |
| Grade 4 | Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids.<br>Consider resuming treatment. |
| Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored.<br>Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind.<br>*Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. | |
| Recommended management: See Endocrine Management Algorithm | |

| **Renal** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Monitor closely and continue therapy. |
| Grade 2 | Hold until ≤ Grade 1. Resume treatment. |
| Grade 3 | Hold until ≤ Grade 1. Resume at discretion of investigator. |
| Grade 4 | Off treatment |

| **Infusion reaction** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Monitor closely and continue therapy. |
| Grade 2 | Hold until ≤ Grade 1. Resume treatment |
| Grade 3 | Hold until ≤ Grade 1. Resume treatment at discretion of investigator. |
| Grade 4 | Off treatment |
| *See Treatment of Nivolumab-Related Infusion* | |

| **Fever** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Evaluate and continue at same dose level |
| Grade 2 | Hold until ≤ Grade 1. Resume treatment. |
| Grade 3 | Hold until ≤ Grade 1. Resume treatment. |
| Grade 4 | Off treatment |
| Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever | |

- Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment.
- Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, Cortrosyn® adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), and thyroxine (T4) must be obtained to document baseline.
- Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.
- Any patient started on corticosteroids initially, who is determined to not require steroid treatment for an autoimmune AE, may resume therapy after a 2-week observation period without further symptoms at the discretion of the PI or investigator.

### 6.3 Dose discontinuation criteria for nivolumab

Treatment with nivolumab should be discontinued in the following cases unless otherwise specified:

- Any Grade 3 or higher infusion-related reactions. Any re-initiation of therapy in this circumstance would require consultation with the PI.

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days
  - Grade 4 lymphopenia or leukopenia < 7 days
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Any drug-related clinically significant adverse event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation.

- Any AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, presents a substantial clinical risk to the participant with continued cabiralizumab and/or nivolumab dosing

## 7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix C for definitions and Appendix D for a grid of reporting timelines.

Adverse events will be tracked from date of consent through 100 days after the last day of study treatment or until time of surgery, whichever occurs first. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- AEs related to surgery
- Grade 1 and 2 hypertension

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 8.1.

## 7.1 Sponsor-Investigator Reporting Requirements

### 7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

### 7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

### 7.1.3 Reporting to Bristol Myers Squibb

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i

- The MedWatch form is available at: MedWatch 3500 Form

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

**SAE Email Address:** Worldwide.Safety@BMS.com
**SAE Facsimile Number:** +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE).

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in Appendix D. It should be sent to MG-RD-GPVE-PHARMACOVIGILANCE@bms.com.

When the file is submitted to BMS, it must be noted the file contains all non-serious adverse events (only adverse events not previously submitted to BMS within the 3 months).

#### 7.1.3.1 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event and complete one of the following forms within 24 hours of awareness of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

### 7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix C for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix C) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix C) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

### 7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 8.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

## 8.0 PHARMACEUTICAL INFORMATION

| **Table 9** | **CA025-018 Study treatments** | | | | |
|---|---|---|---|---|---|
| **Product Description / Class and Dosage Form** | **Potency/Route of Administration** | **Blinded or Open Label** | **IMP or non-IMP** | **Packaging / Appearance** | **Storage Conditions (Per Label) *** |

| Table 9 | CA025-018 Study treatments | | | | |
|---|---|---|---|---|---|
| Nivolumab (BMS-936558-01) Solution for Injection | 100 mg (10 mg/mL) | Open label | IMP | Vial | Refer to the label on container |
| Nivolumab (BMS-936558-01) Solution for Injection | 40 mg (10 mg/mL) | Open label | IMP | Vial | Refer to the label on container |
| Cabiralizumab (BMS-986227) Solution for Injection | 100 mg (20 mg/mL) | Open label | IMP | Vial | Refer to the label on container |
| Cabiralizumab (BMS-986227) Solution for Injection | 140 mg (20 mg/mL) | Open label | IMP | Vial | Refer to the label on container |
| Paclitaxel | | | Non-IMP ** | | |
| Carboplatin | | | Non_IMP ** | | |

* Please refer to the current version of the Investigator Brochures for complete preparation, storage, and handling information.

** Paclitaxel and Carboplatin should be obtained by the investigating site's standard prescribing procedures.

## 8.1 Paclitaxel

### 8.1.1 Product Description

Paclitaxel is obtained via a semi-synthetic process from Taxus baccata. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel Injection, USP is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel Injection, USP is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, USP, 527 mg of purified polyoxyl 35 castor oil, and 49.7% (v/v) dehydrated alcohol, USP.

### 8.1.2 Solution Preparation

Please refer to the package insert for standard preparation instructions.

### 8.1.3 Route of administration

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Administer paclitaxel as an IV infusion over 1 hour.

### 8.1.4 Agent ordering

Paclitaxel is commercially available.

### 8.1.5 Prescribing Information

Please refer to the package insert for full prescribing information on paclitaxel.

## 8.2 Carboplatin

### 8.2.1 Formulation

Carboplatin Injection is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin, USP. Carboplatin, USP is a platinum coordination compound. The chemical name for carboplatin, USP is platinum diamine [1,1-cyclobutanedicarboxylato(2-)-0,0']-,(SP-4-2). Carboplatin, USP is a crystalline powder. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

Each mL of carboplatin injection contains 10 mg of carboplatin, USP in water for injection and is available as a 60 mL multidose vial.

### 8.2.2 Storage

Unopened vials of carboplatin injection are stable to the date indicated on the package when stored at 20° to 25°C (68° to 77°F).

PROTECT FROM LIGHT.

Carboplatin injection multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

#### 8.2.3 Preparation

Carboplatin Injection is a premixed aqueous solution of 10 mg/mL carboplatin.

Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin aqueous solutions be discarded 8 hours after dilution.

#### 8.2.4 Route of Administration

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Administer paclitaxel as an IV infusion over 1 hour.

#### 8.2.5 Agent ordering

Carboplatin is commercially available.

#### 8.2.6 Prescribing Information

Please refer to the package insert for full prescribing information on carboplatin.

### 8.3 Nivolumab

#### 8.3.1 Nivolumab Description

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of:

- patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab

- patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy
- patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy
- patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy
- patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after:
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy
- patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab
- patients with hepatocellular carcinoma who have been previously treated
- with sorafenib

It is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

### 8.3.2 Clinical Pharmacology

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

### 8.3.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

### 8.3.4 Supplier

Nivolumab will be supplied by Bristol Myers Squibb.

### 8.3.5 Dosage Form and Preparation

Nivolumab will be provided either as a 100 mg/10 mL (10 mg/mL) solution in a single-use vial or a 40 mg/4 mL solution in a single-use vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

### 8.3.6 Storage and Stability

The product does not contain a preservative.

After preparation, store the nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

### 8.3.7 Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

## 8.4 Cabiralizumab

Note that no patients enrolled after implementation of Amendment 7 (following the conclusion of the safety lead-in) will receive cabiralizumab.

### 8.4.1 Cabiralizumab Description

Cabiralizumab is a polypeptide that comprises of 2 heavy chains and 2 light chains and is a recombinant, humanized IgG4 monoclonal antibody that targets human CSF1R. Cabiralizumab is produced from cell culture using a Chinese Hamster Ovary (CHO) cell line.

### 8.4.2 Clinical Pharmacology

Cabiralizumab is a recombinant, humanized IgG4 mAb that binds to human CSF1R. Binding of cabiralizumab to CSF1R antagonizes binding of CSF1 and IL34, the 2 ligands to CSF1R, thereby preventing activation of CSF1R. Cabiralizumab contains a single amino acid substitution in the hinge region to prevent hemi-dimer exchange.

### 8.4.3 Pharmacokinetics and Drug Metabolism

No in vitro or in vivo metabolism studies have been conducted using cabiralizumab. In accordance with the regulatory guidelines for biotechnology-derived pharmaceuticals, the expected in vivo degradation of mAbs is to small peptides and amino acids via biochemical pathways that are generally understood and independent of typical small-molecule drug-metabolizing enzymes.

### 8.4.4 Supplier(s)

Cabiralizumab will be provided by Bristol Myers Squibb.

### 8.4.5 Dosage Form and Preparation

The 2 formulations of cabiralizumab injection available for clinical use are as described below.

Cabiralizumab Injection, 100 mg/Vial (20 mg/mL) (Formulation 2)
Cabiralizumab injection is a colorless to pale yellow liquid, clear to slightly opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 20 mg/mL in L-histidine, L-histidine hydrochloride monohydrate, sucrose, edetate disodium dihydrate, polysorbate 80, and water for injection at pH 6.5. Diluted solutions of hydrochloric acid and/or sodium hydroxide maybe used for pH adjustment. The drug product includes a 0.58-mL overfill to account for vial, needle, and syringe holdup. It is supplied in a 5-cc Type I flint glass vial, stoppered with a fluoropolymer film-laminated rubber stopper, and sealed with aluminum seal.

Cabiralizumab Injection, 140 mg/Vial (20 mg/mL)
Cabiralizumab injection is a colorless to pale yellow liquid, clear to slightly opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 20 mg/mL in L-histidine, L-histidine hydrochloride monohydrate, sucrose, edetate disodium dihydrate, polysorbate 80, and water for injection at pH 6.2-7.0. Diluted solutions of hydrochloric acid and/or sodium hydroxide maybe used for pH adjustment. The drug product includes a 0.6-mL overfill to account for vial, needle, and syringe holdup. It is supplied in a 10-cc Type I flint glass vial, stoppered with a fluoropolymer film-laminated rubber stopper, and sealed with aluminum seal.

Cabiralizumab injection is to be administered as an IV infusion through a low-protein-binding polyethersulfone membrane, 0.2-µm in-line filter at the protocol-specified doses and infusion times. Cabiralizumab injection can be infused undiluted (20 mg/mL) or diluted with 0.9% sodium chloride injection or 5% dextrose injection to protein concentrations as low as 1.0 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Detailed instructions for drug product dilution and administration are provided in the pharmacy manual for the clinical study.

For both formulations, care must be taken to ensure sterility of the prepared solution because the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between cabiralizumab injection and PVC or polyolefin infusion bags with DEHP-free infusion sets have been observed.

### 8.4.6 Storage and Stability

Cabiralizumab Injections
Vials of cabiralizumab injections must be stored at 2°C to 8°C (36°F to 46°F), protected from light, and must not be frozen.

Undiluted Cabiralizumab Injections and Diluted Cabiralizumab Injections in the IV Bag

The administration of cabiralizumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, protected from light and a maximum of 4 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

### 8.4.7 Administration

Refer to Section 6.3.

## 9.0 CORRELATIVE STUDIES

To assess the effects of cabiralizumab in combination with chemotherapy and nivolumab on the tumor, blood and bone marrow microenvironment of patients with triple-negative breast cancer as measured by:

a. Correlation of TILs (CD8+), TAMs (**CD163+**), CSF-1R+ cells content with clinical activity (CSF-1R+ biomarker, CXCR-1 expression, and other M1 and M2 CD206, Iba1 biomarkers to assess target engagement of cabiralizumab for patients who participated in the safety lead-in only).
b. Tumor infiltrating lymphocytes (TILs) pre, during and post therapy. Intra tumoral T cell composition (CD8/CD4 ratio) pretreatment and on-treatment (4-weeks of therapy). We expect the CD8/CD4 ratio to increase with treatment.
c. Tumor associated macrophages (TAMs) pre, during and post therapy.
d. Correlation of immunosuppressive cytokine levels secreted by TAMs with TAM content, TILs and response to therapy.
e. Correlation of other tumor associated immune cells with treatment response
f. Analysis of nonclassical and classical monocyte content in peripheral blood

From the breast tumor, bone marrow and peripheral blood samples, we will determine:

- Breast Tumor Tissue:
  - M2 TAM content (CD68+/CD163+, CSF1R+) by IHC (CSF-1R+ biomarker for patients who participated in the safety lead-in only)
  - TILs and PD-L1 levels by IHC
  - CD4+ and CD8+ TIL content by histology.
  - FoxP3+ T regulatory cells and dendritic cell (DC) content by IHC.
  - Detailed tumor, immune cell and stromal cell characteristics could be obtained at each time point using sophisticated imaging analysis. Multiplexed fluorescence microscopy (MxIF) system developed for quantitative, single-cell, and subcellular characterization of multiple analytes in single FFPE tissue. MxIF will address tumor-microenvironment

heterogeneity while the integration of MxIF with clinical data will provide a comprehensive picture on treatment responses.

- Bone Marrow Aspirate:
  - MDSC and DC content by flow cytometry
  - Disseminated tumor cell (DTC) gene signature

- Peripheral Blood:
  - CSF1, IL-34, IL-8, other cytokines (ELISA). Plasma CSF-1 and IL-34 concentrations are expected to increase with cabiralizumab treatment. (CSF-1R+ biomarker for patients who participated in the safety lead-in only)
  - Non-classical monocytes (CD14+ CD16++) by flow cytometry. Nonclassical monocytes are expected to decrease after cabiralizumab treatment. Classical CD14+CD16- monocytes are not expected to change substantially. (CSF-1R+ biomarker for patients who participated in the safety lead-in only)
  - Circulating T lymphocytes, MDSC and DC by flow cytometry
  - Circulating tumor cells
  - Circulating tumor DNA
  - Bone turnover biomarkers
  - Storage for future studies

Expression profiling correlative endpoints
1. Cryopreserved bone marrow and tissue biopsies will be subjected to bulk DNA/RNA sequencing to access cell composition and mutational burden.
2. Cryo-preserved bone marrow and fresh biopsies will be subjected to single cell RNAseq to determine immune cell compositions.

## 9.1 Tumor Biopsy

### 9.1.1 Collection of Specimens

Research biopsies will be performed at baseline, Week 5, definitive surgery, and at time of relapse (optional). If a patient discontinues protocol therapy and receives SOC neoadjuvant therapy prior to surgery, the bone marrow, tissue and blood should not be collected. If a patient discontinues protocol therapy due to toxicity and/or other reasons and does not receive SOC neoadjuvant therapy, the bone marrow, tissue and blood should be collected. Guidelines are below.

### 9.1.2 Tumor Biopsies

Four cores (with a 14-gauge needle) of tumor tissue will be collected at pre-treatment (preferable at the time of port-a-cath placement), on-treatment at week 5 and at the time of surgery. Biopsies will be performed at pre-treatment and on-treatment (week 5). At surgery, the cores will be collected from the surgical specimen. At time of recurrence a biopsy will be collected (optional).

| | |
|---|---|
| Baseline | During screening, preferably at same time as port-a-cath placement |
| Week 5 | On-treatment biopsy after 2 cycles of nivolumab +/- cabiralizumab. |
| Surgery | At the time of definitive surgery. Cores will be collected from the surgical specimen. |
| Disease Progression | Optional |

### 9.1.3 Handling of Specimens

Four cores will be collected at each time point and processed as described below:

1) First Core—in 10% formalin and TPC creates FFPE block for IHC analysis of immune cells
2) Second Core— placedin media and put on wet ice and transported to investigators lab (DeNardo)
3) Third Core—in saline for snap freezing at the TPC for possible use in proteomics
4) Fourth Core—in saline for cell dissociation and cryopreservation of cells for banking/future use at by TPC.

All samples should be taken to the Siteman Cancer Center Tissue Procurement Core (TPC) for processing, assignment of accession number and storage until time of analysis:

Siteman Cancer Center Tissue Procurement Facility
425 S. Euclid Ave., Rm 5120
St. Louis, MO 63110
Phone: 314-454-7615
Fax: 314-454-5525
Email: tbank@pathology.wustl.edu

### 9.1.4 Specimen Storage

After processing, FFPE, fresh and frozen cores will be stored at the TPC until time of analysis.

## 9.2 Bone Marrow

### 9.2.1 Collection of Specimens

Two EDTA tubes (10 mL each) of bone marrow aspirate will be collected, 1 tube from each iliac crest at the following time points:

- Time of port placement (baseline)

- Time of surgery
- Disease progression (optional)

### 9.2.2 Handling of Specimens

Specimens will be handled per instructions on the TPC submission forms using the TPC SOP or per the Aft lab SOPs.

### 9.2.3 Specimen Storage

Specimen storage will be addressed per instructions in the TPC submission forms using the TPC SOP or per the Aft lab SOPs.

## 9.3 Blood Draw

### 9.3.1 Collection of Specimens

Four EDTA tubes each containing 8-10 mL of blood and 1 red/tiger top tube (without additive or gel) containing 5-10 mL of blood will be collected at the following time points:

| Time point | Instructions | Tube type(s) | Blood volumes |
|---|---|---|---|
| Baseline | Prior to Week 1 treatment | 4 EDTA tubes<br><br>1 red/tiger top tube (without additive or gel) | 8-10 mL blood each<br><br>5-10 mL blood each |
| Week 2 | Prior to Week 2 treatment | 3 EDTA tubes | 8-10 mL blood each |
| Week 3 | Prior to Week 3 treatment | 3 EDTA tubes | 8-10 mL blood each |
| Week 5 | After 4 weeks of chemo + nivolumab +/- cabiralizumab +/- 3 days of mandatory tumor biopsy | 4 EDTA tubes<br><br>1 red/tiger top tube (without additive or gel) | 8-10 mL blood each<br><br>5-10 mL blood each |
| Week 10 | Prior to Week 10 treatment | 3 EDTA tubes | 8-10 mL blood each |
| Prior to surgery | After completion of treatment prior to surgery (no more than 7 days prior to time of surgery) | 4 EDTA tubes<br><br>1 red/tiger top tube (without additive or gel) | 8-10 mL blood each<br><br>5-10 mL blood each |

| | | | |
|---|---|---|---|
| Post-surgery follow-up | At standard of care post-surgery follow-up appointment typically 3-4 weeks post-surgery but may be shorter or longer. | 4 EDTA tubes<br><br>1 red/tiger top tube (without additive or gel) | 8-10 mL blood each<br><br>5-10 mL blood each |
| Disease progression | Optional | 4 EDTA tubes<br><br>1 red/tiger top tube (without additive or gel) | 8-10 mL blood each<br><br>5-10 mL blood each |

### 9.3.2 Handling of Specimens

Specimens will be handled per instructions TPC or Aft lab SOPs.

## 10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

| Case Report Form | Submission Schedule |
|---|---|
| Original Consent Form | Prior to registration |
| On-Study Form<br>Medical History Form | Prior to starting treatment |
| Treatment Form | Weekly |
| Toxicity Form | Continuous |
| Treatment Summary Form | Completion of treatment |
| Surgery Form | Time of surgery |
| Correlatives Form | Baseline, Week 2, Week 3, Week 5, Week 10, time of surgery, post-surgery follow-up (blood draw only),time of recurrence |
| Follow Up Form | 6 months and 12 months after surgery, Year 2, Year 3, Year 4, Year 5 |
| MedWatch Form | See Section 7.0 for reporting requirements |
| Progression Form | Time of progression |
| Death Form | Time of death |

### 10.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

### 10.2 Concomitant Medication Collection in the Case Report Forms

All concomitant medications should be recorded for the first six patients enrolled to each arm. Beginning with enrollment with the seventh patient of each arm only medications taken regularly are required to be collected.

## 11.0 MEASUREMENT OF EFFECT

### 11.1 Surgery

A pathologic complete response (pCR) is defined as no histology evidence of invasive tumor cells in the surgical breast specimen and sentinel or axillary lymph nodes.

### 11.2 Post-surgery

Local recurrence is defined as histologic evidence of ductal carcinoma in situ or invasive breast cancer in the ipsilateral breast or chest wall.

Regional recurrence is defined as the cytologic or histologic evidence of disease in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or soft tissue of the ipsilateral axilla.

Distant recurrence is defined as the cytologic, histologic, and/or radiographic evidence of disease in the skin, subcutaneous tissue, lymph nodes (other than local or regional metastasis), lung, bone narrow, central nervous system or histologic and/or radiographic evidence of skeletal or liver metastasis.

Second primary breast cancer is defined histologic evidence of ductal carcinoma in situ or invasive breast cancer in the contralateral breast or chest wall.

Second primary cancer (non-breast) is defined as any non-breast second primary cancer other than squamous or basal cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the cervix is to be reported and should be confirmed histologically whenever possible.

## 12.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

## 13.0 STATISTICAL CONSIDERATIONS

### 13.1 Study Design

As of July 1, 2022, 12 patients have been enrolled to the study in the safety lead-in. Due to the expiration of cabiralizumab, Amendment 7 was activated to remove the cabiralizumab

arm. Accordingly, the statistical considerations of the protocol have been changed as follows:

The original design of a phase II randomized two-arm study has been updated to a phase II single arm study where a total of **N=25 eligible and primary-endpoint evaluable** patients with clinical stage II/III TNBC will receive SOC chemo + nivolumab. The primary endpoint remains the same (percent change of on-treatment TAMs from baseline and percent change of on-treatment TILs from baseline), but there will no longer be a comparison between TAM and TIL percent change between patients who receive cabiralizumab and patients who don't.

As of July 1, 2022, 6 evaluable patients have been enrolled to the SOC chemo + nivolumab arm (and 6 patients were enrolled to the now-discontinued cabiralizumab arm). Following the approval and activation of Amendment 7, we will continue to recruit an **additional 19 evaluable** patients (**for a total of N=25 evaluable patients**) to the SOC chemo + nivolumab arm in this study.

## 13.2 Objectives

The primary objective is to compare on-treatment TAMs and TILs (Week 5) against their baseline levels. It is hypothesized that the on-treatment TAMs and TILs will improve compared with baseline levels with reduced TAMs and increased TILs post treatment.

The secondary objectives are:

- to estimate the pCR rate in this study
- to determine recurrence-free survival
- to estimate the grade 3 or higher treatment related adverse event (AE) rate
- to compare TAM and TILs percent change between patients who achieve pCR vs. those who didn't. It is hypothesized that patients who do not achieve pCR may have increasing TAMs or/and reduced TILs.

## 13.3 Endpoints

The co-primary endpoints are percent (%) change of on-treatment TAMs from baseline and percent (%) change of on-treatment TILs from baseline. Stromal TIL score is defined as the percentage of tumor stroma area that was occupied by mononuclear inflammatory cells.

The secondary endpoints include:

- pathological complete response (pCR) rate
- adverse events, especially grade 3 or higher treatment related AE rate
- recurrence-free survival (RFS), defined from date of surgery to the earliest time of recurrence, time to development of a second cancer, or time of death from any cause.

## 13.4 Statistical hypothesis

The overall alpha level is set at 5% and we evenly split the alpha level on TAM and TILs, each with alpha=2.5%.

We will simultaneously test the following hypotheses for the primary endpoint TAM.

H1: reduction in % change of on-treatment TAMs $\neq 0$

vs.

H0: reduction in % change of on-treatment TAMs = 0

and for TILs,

H1: increase in % change of on-treatment TILs $\neq 0$

vs.

H0: increase in % change of on-treatment TILs = 0

### 13.5 Sample size for the primary endpoint

A one-stage design based on one-sample normal test was used to achieve 80% power at alpha=2.5% for each of the two co-primary endpoints for the phase II single arm study to test the on-treatment vs. baseline TAM and TIL percentage change against a null value of 0.

According to Loi (2019 JCO), the average (SD) of stromal TILs and intratumor TILs at diagnosis is 0.23 (0.2) and 0.053 (0.1), respectively, for TNBC patients at time of diagnosis. Chemotherapy has been reported to decrease TILs. We assume that on-treatment stromal TILs in Arm A has a mean (SD) of 0.2 (0.3).

According to Ries et al (Figure 6B top panel on TAM marker CD68+/CD163+, 2019 Cancer Cell), the % change from BL of TAM was estimated at around -0.57 with a standard deviation (SD) around 0.28, under the treatment of chemo plus anti-CSF-1R inhibitor.

We conservatively assume an averaged percent change of on treatment TAM from baseline is about -20% with a SD of 0.3. Similarly, the TILs % change from baseline is expected at least 20% with a SD of 0.3. N=25 patients allows 81.98% power to test an averaged percent change of on treatment TAMs from baseline estimated about -20% and an averaged percent change of on treatment TILs from baseline estimated about 20%, assuming a standard deviation of 0.3, based on simultaneous 2-sided 1-sample normal test at alpha=2.5%.

The 6 patients enrolled in Arm A (chemo + nivolumab) during the safety lead-in are included towards the total N=25 evaluable patients enrolled to this study and thus we need to enroll an additional 19 patients after approval and activation of Amendment 7.

## 13.6 Sample size for the secondary endpoint pCR rate

The total sample size of **N=25** allows to estimate a hypothesized pCR rate of **0.55** for this study with a 95% CI of 0.362~0.725.

## 13.7 Sample size for comparing TAM and TILs percentage change by pCR status

For the secondary objective of comparing % change of TAMs and TILs between patients with pCR versus non-pCR, we hypothesize that patients with non-pCR have higher % change of TAMs or/and lower % change of TILs at on-treatment relative to baseline, when compared with patients with pCR. We expect among N=25, 12/13 patients with/without pCR, allowing 80% power to detect a mean difference effect size of 1.17 for either TAM or TILS between the two patient groups, based on 2-sided 2-sample normal test at alpha=5%.

## 13.8 Data analysis

All data on the chemo+nivolumab treatment group will be analyzed as recorded and no data imputation will be performed. Baseline demographic, clinical-pathological and lab tests will be summarized using summary statistics. For summary statistics, continuous variables will be summarized with mean/median and standard deviation/inter-quartile range at each time point. Qualitative variables will be summarized by counts and percentages.

Data from the 6 patients enrolled in the discontinued Arm B (chemo + nivolumab + cabiralizumab) during the safety lead-in will be analyzed as described in Section 13.8.9.

### 13.8.1 Baseline Characteristics and Demographic Variables

Demographic data (e.g., age, gender, race, height, weight and ethnicity), medical history, prior treatments, and baseline disease characteristics, including primary tumor location, stage of disease and performance status, will be summarized among all or by patient subsets (e.g.,pCR vs. non-pCR).

### 13.8.2 Data Analysis for TAMs and TILs

TAM and TILs at baseline and post treatment will be separately summarized by descriptive statistics including mean, median, interquartile range, standard deviation, overall and by pCR status. For testing the percent change of on-treatment TAMs and on-treatment TILs from baseline, the paired sample t-test or Wilcoxon signed rank sum will be used as proper. For TAM and TILs percent change difference between pCR vs. non-pCR, two sample t-test or Wilcoxon rank sum test will be used as proper.

### 13.8.3 Data Analysis for grade 3 or higher treatment related AE rate

The toxicity profiles will be graded according to CTCAE v5 and listed by organ class. Worst grade toxicity will be tabulated as counts and frequencies, overall, by grades and by patient characteristics. Rate of grade 3 or higher all type and immune-related toxicities relevant to the study drugs will be calculated with 95% exact Clopper-Pearson confidence interval (CI) overall and by patient subset and will be compared between patients subset by Fisher's exact test. The grade 3 or higher treatment related AE rate (or equivalently, the grade 3 or higher treatment related AE free rate) will be estimated with 95% Wilson-type CI and tested against the null rate of 75% by 1-sample proportion test based on normal approximation.

### 13.8.4 Data Analysis for pCR

The pCR rate will be estimated with 95% Wilson-type CI.

### 13.8.5 Data Analysis for the DTC elimination and BM status

DTC elimination rate at time point from BL will be calculated as the percentage of BL DTC+ patients who achieved DTC- on or after neoadjuvant treatment at surgery. BM test positive rate will be calculated as % of patients whose bone marrow sample tested positive. DTC elimination rate and BM rate will be calculated at each post-treatment time point, overall and by patient subset separately, accompanied with 95% exact Clopper-Pearson CI. Fisher's exact test will be used to compare the rate difference.

### 13.8.6 Data Analysis for the RFS

RFS will be analyzed by the Kaplan-Meier method to estimate empirical survival probability overall and median PFS with 95% Brookmeyer and Crowley confidence intervals. The survival difference between patient subsets will be compared by log rank test. The covariate-adjusted Cox proportional hazard model will be applied to estimate the hazard ratio between patient groups when other covariates (classical demographic and clinic-pathological variables for breast cancer) are considered.

### 13.8.7 Correlative study data analysis

Median curve with 95% CI will be derived for the pre, during and post-treatment TAMs and TILs. TILs and TAMs at pre, during and post-treatment will be each summarized by descriptive statistics and each, as well % change, will be compared between patient subsets (e.g., pCR vs. residual disease) by two sample t-test or Wilcoxon rank sum test as appropriate. TILs and TAMs between time points will be compared by paired sample t-test or Wilcoxon signed rank test as appropriate. Inflammatory gene expression data will be compared by two sample t-test or Wilcoxon rank sum test as appropriate. Across time points, TILs and TAMs will

each be integratively analyzed by linear mixed effects model fitting TILs or TAMs on patient characteristics, treatment response and potentially their interactions. Multiple testing will be controlled for false discovery rate. TIL/TAM ratios will be derived and similarly analyzed.

#### 13.8.8 Analysis of TAMs and TILs on Arm B patients

For the 6 patients already enrolled to the discontinued SOC chemo + nivolumab + cabiralizumab arm, we will summarize the toxicity data as previously described for the SOC + nivolumab treatment patients. TAMs and TILs will be summarized by descriptive statistics as appropriate.

### 13.9 Futility monitoring plan

There is no futility stopping rule due to the initial signal of efficacy for the first 6 patients enrolled in the nivolumab + chemotherapy arm and recent pCR data with a similar neoadjuvant regimen[65].

### 13.10 Safety stopping rule

Given the safety results from KEYNOTE-522, safety concerns mandating early stopping of the trial are not expected, as this study will only use two chemotherapeutic drugs while KEYNOTE-522 used four chemotherapeutic drugs.

Further, all grade 2 and 3 immune-related adverse events in addition to all grade 4 and 5 adverse events will be reviewed at each regularly scheduled study conference call. In the event of any concerns related to excessive treatment-related adverse events, enrollment will be temporarily discontinued and all available data on adverse events will be assessed by a review committee in order to make a recommendation of continuation of accrual, suspension followed by formal amendment and reactivation, or study closure.

### 13.11 Definitions of Study Populations for Analysis

#### 13.11.1Safety Population

The safety population will consist of all subjects who receive any amount of study immunotherapy drug. Analyses based on safety population will be performed according to the actual treatment received for the length of the study. Data handling rules for subjects in the experimental/control arm who received incorrect study treatment will be described in the SAP.

#### 13.11.2 pCR evaluable patients

Patients are evaluable if patients satisfy inclusion criteria and have pCR results (either had surgery or have documented disease progression prior to surgery).

#### 13.11.3 TAM and TILs evaluable patients

Patients are considered evaluable for the primary objective if they satisfy eligibility criteria, have received at least 2 doses of the total immunotherapeutic drug dosage, and have valid baseline and on-treatment TAMs and TILs measurements for a percent change evaluation of TAMs and TILs.

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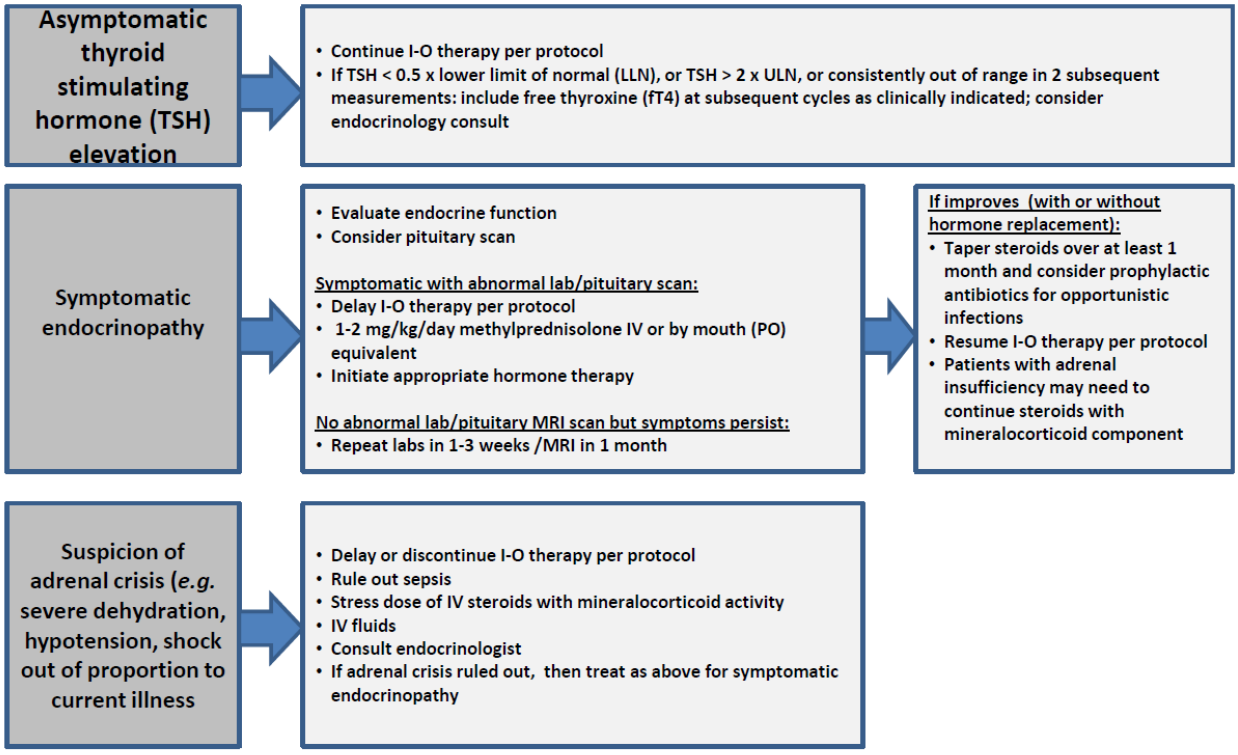
**APPENDIX A: ECOG Performance Status Scale**

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## APPENDIX B: Management Algorithms for Endocrinopathy, Gastrointestinal, Hepatic, Neurological, Pulmonary, Renal, and Skin Adverse Events

### Endocrinopathy Management Algorithm

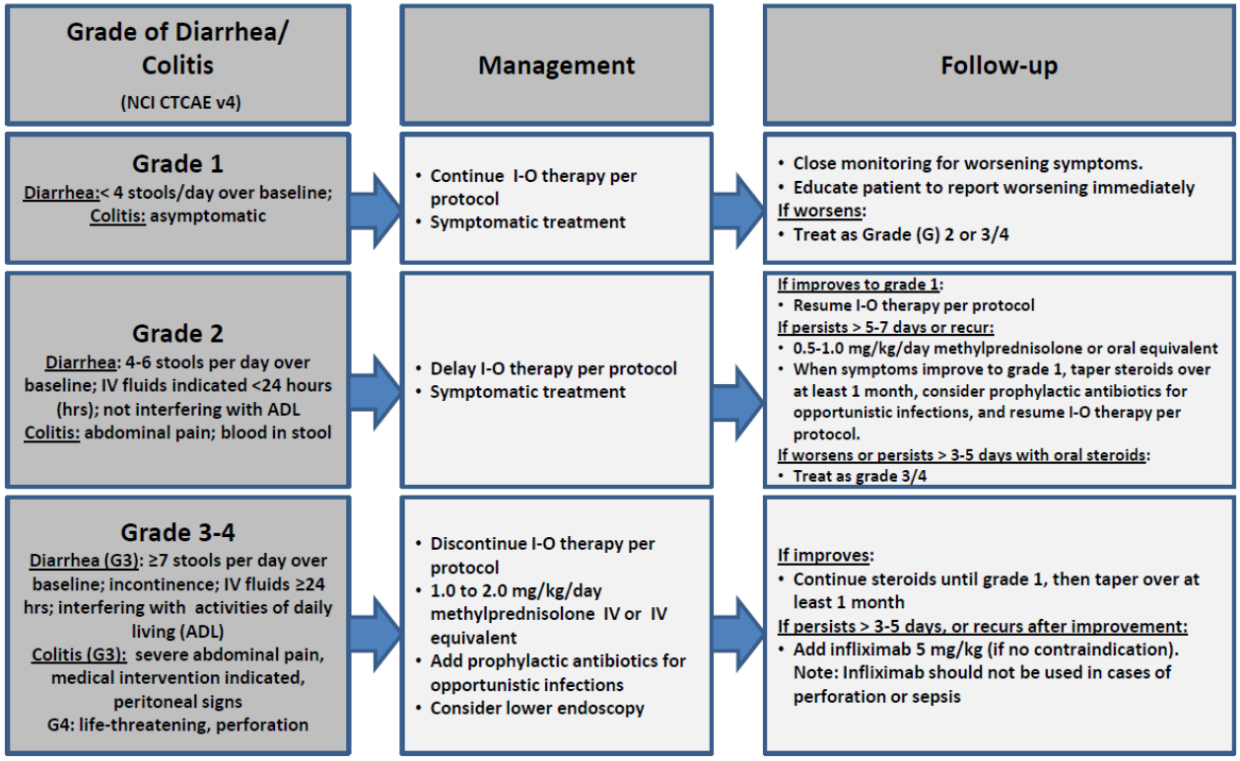
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy. Consider visual field testing, endocrinology consultation, and imaging.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# GI Adverse Event Management Algorithm

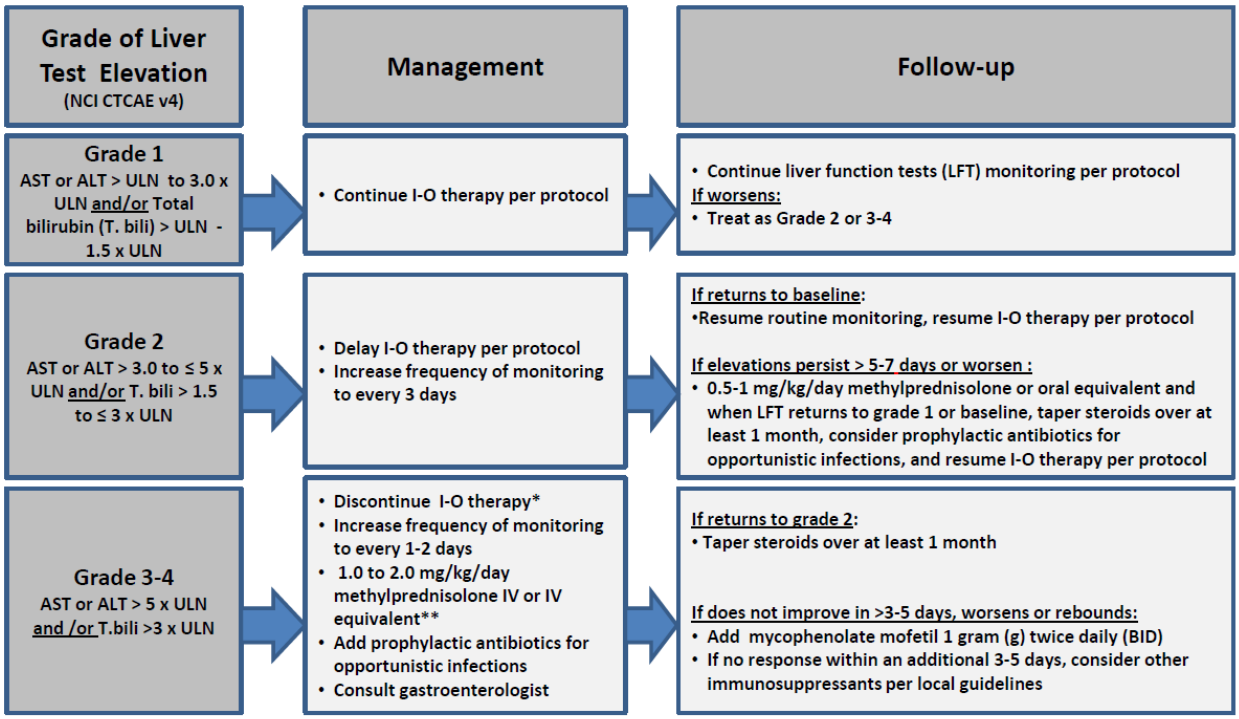
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



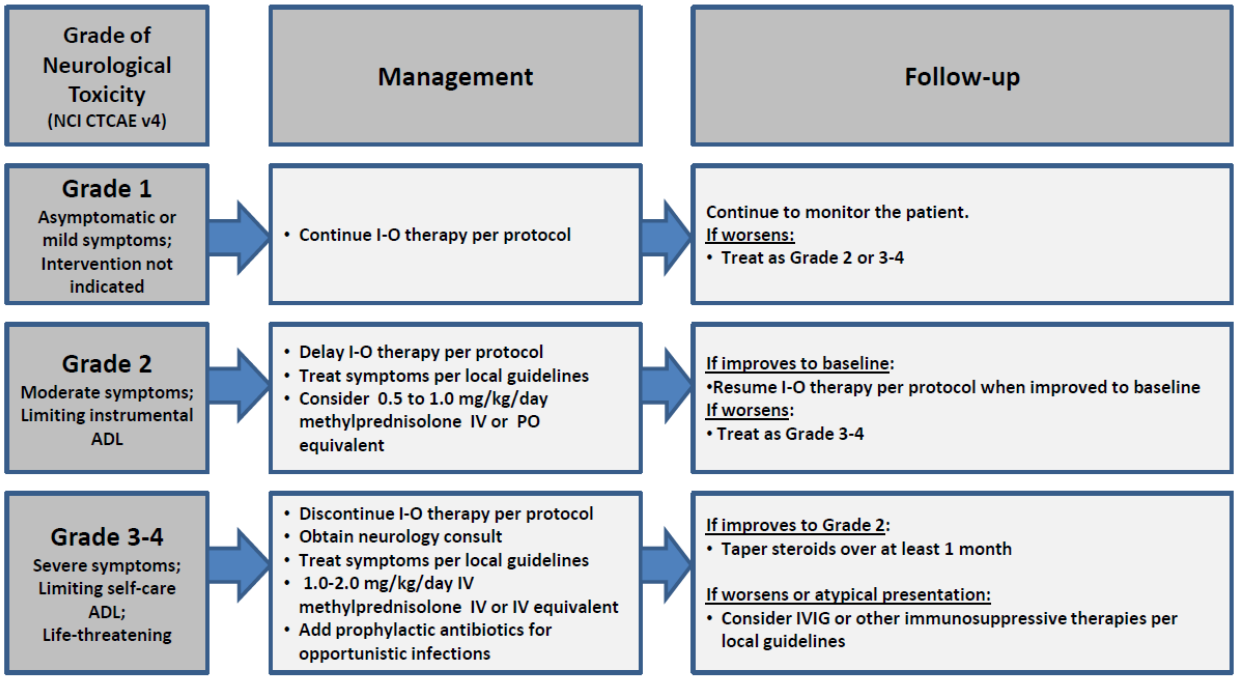

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

# Neurological Adverse Event Management Algorithm

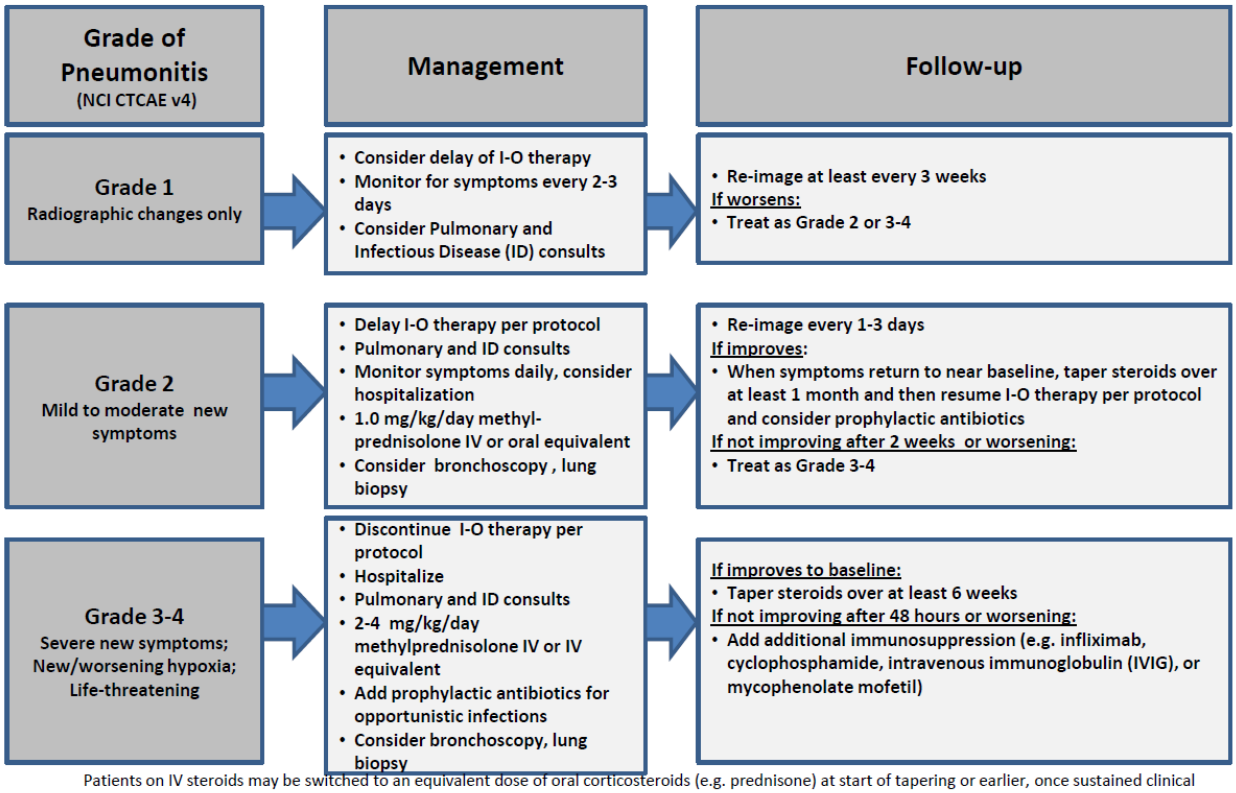
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Pulmonary Adverse Event Management Algorithm

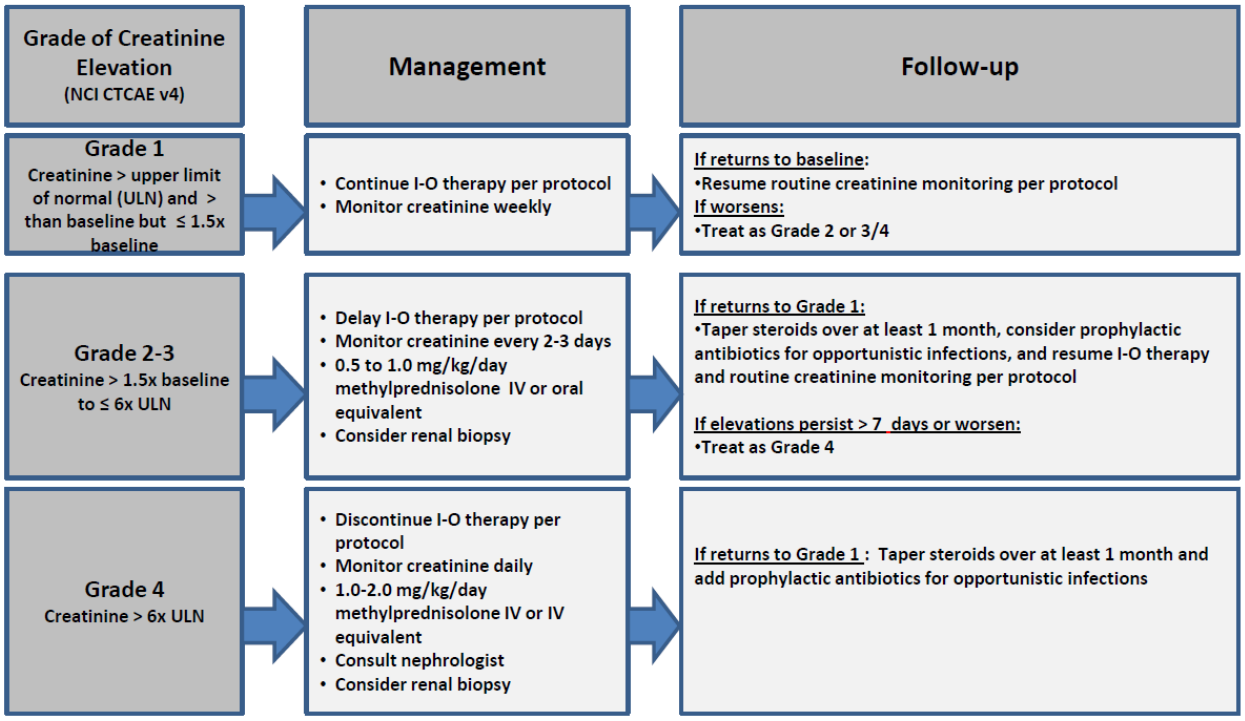
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Renal Adverse Event Management Algorithm

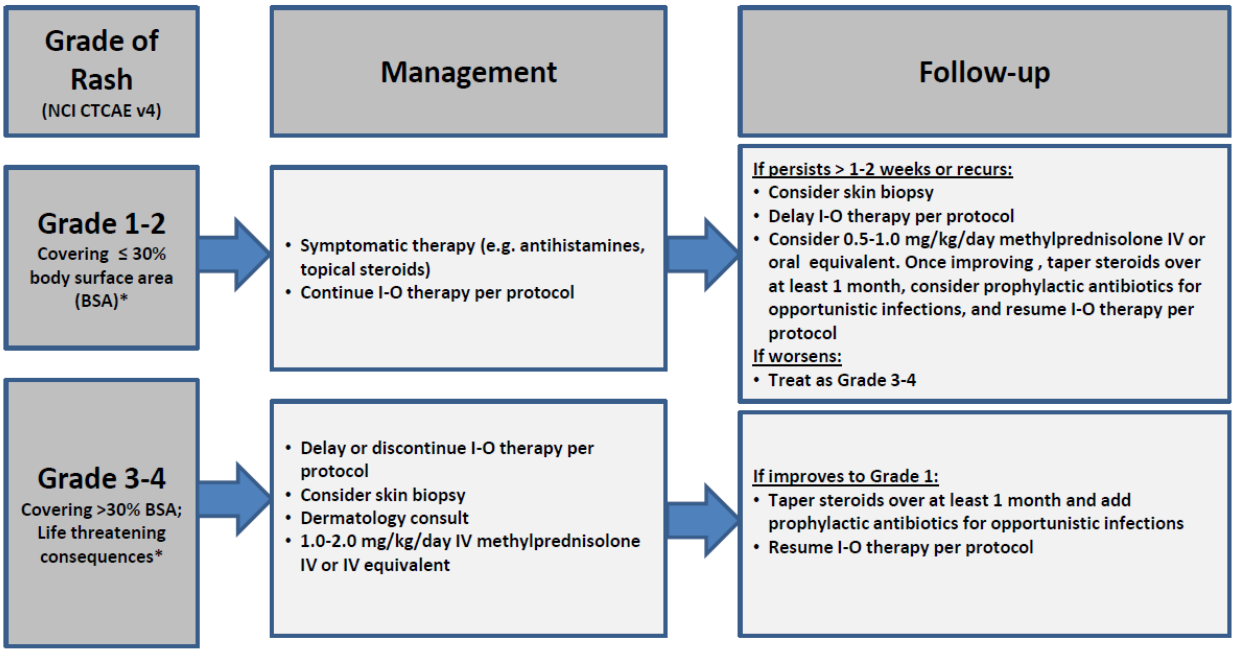
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

# Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

## APPENDIX C: Definitions for Adverse Event Reporting

### A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

**Definition:** any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

**Grading:** the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

**Attribution (relatedness), Expectedness, and Seriousness:** the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

### B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

**Definition:** any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

**Definition:** any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

**Definition:** an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

## E. Protocol Exceptions

**Definition:** A planned change in the conduct of the research for one participant.

## F. Deviation

**Definition:** Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

## G. Potential Drug-Induced Liver Injury

**Definition:** Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   **AND**
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   **AND**
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

## APPENDIX D: Reporting Timelines

| Expedited Reporting Timelines | | | | |
|---|---|---|---|---|
| **Event** | **HRPO** | **QASMC** | **FDA** | **Bristol Myers Squibb** |
| Serious AND unexpected suspected adverse reaction | | | Report no later than 15 calendar days after it is determined that the information qualifies for reporting | |
| Serious adverse events (regardless of relatedness) and all occurrences of potential DILIs | | | | Report within 24 hours/1 business day of becoming aware of the event |
| Unexpected fatal or life-threatening suspected adverse reaction | | | Report no later than 7 calendar days after initial receipt of the information | |
| Unanticipated problem involving risk to participants or others | Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. | Report via email after IRB acknowledgment | | |
| Pregnancy | | | | Report within 24 hours/1 business day of becoming aware of the event |
| Major deviation | Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. | | | |
| A series of minor deviations that are being reported as a continuing noncompliance | Report within 10 working days. | | | |
| Protocol exception | Approval must be obtained prior to implementing the change | | | |
| Clinically important increase in the rate of a serious | | | Report no later than 15 calendar days after it is determined that | |

| Expedited Reporting Timelines | | | | |
|---|---|---|---|---|
| **Event** | **HRPO** | **QASMC** | **FDA** | **Bristol Myers Squibb** |
| suspected adverse reaction of that list in the protocol or IB | | | the information qualifies for reporting | |
| Complaints | If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review. | | | |
| Breach of confidentiality | Within 10 working days. | | | |
| Incarceration | If withdrawing the participant poses a safety issue, report within 10 working days.<br><br>If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review. | | | |

| Routine Reporting Timelines | | | | |
|---|---|---|---|---|
| **Event** | **HRPO** | **QASMC** | **FDA** | **Bristol Myers Squibb** |
| Adverse event or SAE that does not require expedited reporting | If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review | Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months. | The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report. | SAE Reconciliation: the clinical database AE cases transmitted to BMS Global Pharmacovigilance will be reconciled every 3 months to verify and confirm all SAEs have been transmitted.<br><br>AEs that are routinely collected according to GCP shall be submitted to BMS every 3 months by the last working day of the third month. Data points to be sent include date entered, BMS study number, subject ID, site subject, gender, age, race, drug name, visit, study day, days on drug |

| Routine Reporting Timelines | | | | |
|---|---|---|---|---|
| **Event** | **HRPO** | **QASMC** | **FDA** | **Bristol Myers Squibb** |
| | | | | at AE start, MedDRA preferred term, investigator verbatim term, AE start date, AE stop date, event duration, intensity, relationship, action taken, outcome, concomitant medications, and medical history.<br><br>The AE information is required to be sent in an Excel file named BMS CA025-018_DD-MMM-YYYY.xls. When the file is submitted to BMS, it must be noted the file contains all non-serious adverse events (only AEs not previously submitted to BMS within the previous 3 months). |
| Minor deviation | Report summary information at the time of continuing review. | | | |
| Complaints | If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review. | | | |
| Incarceration | If withdrawing the participant poses a safety issue, report within 10 working days.<br><br>If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review. | | | |