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ABLE: PHASE 2, SINGLE ARM, TWO-STAGE STUDY OF ABRAXANE WITH ANTI-PD1/PDL1 IN PATIENTS WITH ADVANCED UROTHELIAL CANCER

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Study Drug: nab-paclitaxel (Abraxane) – Investigational

Other Drug: Pembrolizumab (Keytruda®) – Standard of care

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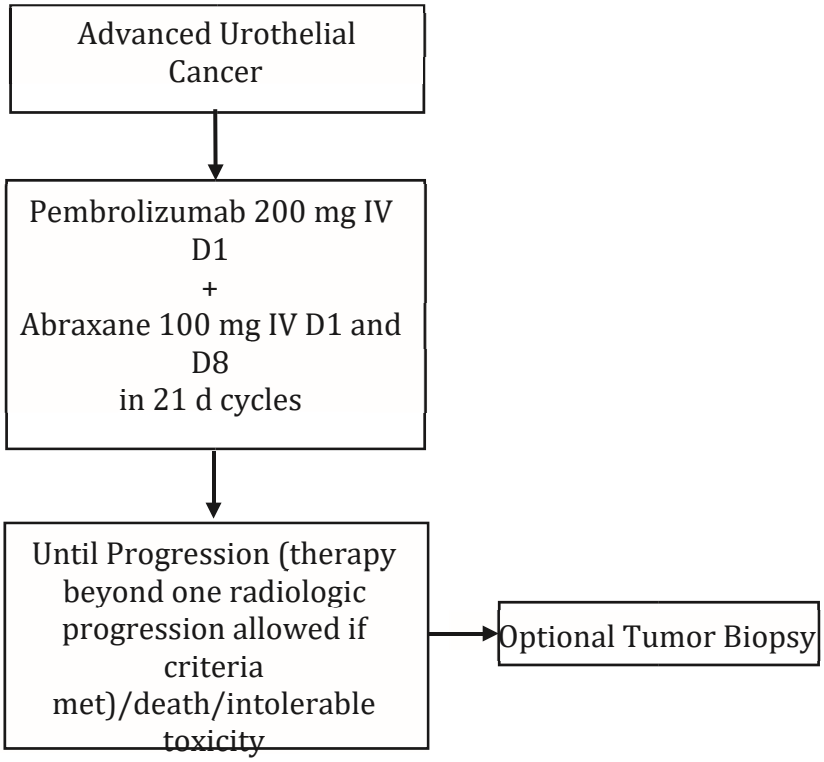
ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
Anti-PD1/PDL1	Pembrolizumab for purposes of this protocol
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
SAE	Serious Adverse Event

SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
UaP	Unanticipated Problem
UMCCC	University of Michigan Comprehensive Cancer Center
WBC	White Blood Cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	ABLE: PHASE 2, SINGLE ARM, TWO-STAGE STUDY OF ABRAXANE WITH ANTI-PD1/PDL1 IN PATIENTS WITH ADVANCED UROTHELIAL CANCER
Phase	II
Methodology	Single arm
Study Duration	24 months of accrual; up to 24 months of follow-up per subject/death
Study Center(s)	Single center

Objectives and Endpoints	**OBJECTIVES:** • PRIMARY: • To determine the efficacy of pembrolizumab and abraxane in patients with advanced urothelial cancer. • SECONDARY: • To assess the safety and toxicity of pembrolizumab and abraxane in patients with advanced urothelial cancer. • To estimate secondary measures of efficacy with pembrolizumab and abraxane in patients with advanced urothelial cancer. • CORRELATIVE: • To correlate PD-L1 expression on tumor cells and TILs in baseline archival tumor tissue with primary and secondary efficacy measures. • EXPLORATORY: • To develop a therapy response predictor based on baseline immune parameters in tumor tissue. • To determine the quality of life of patients enrolled on the study as reflected in patient-reported outcomes **ENDPOINTS:** • PRIMARY: • ORR (Overall Response Rate) proportion in patients with advanced urothelial carcinoma treated with pembrolizumab and abraxane. • SECONDARY: • Adverse events by CTCAE criteria of the pembrolizumab and abraxane combination in patients with advanced urothelial carcinoma. • PFS (Progression-Free Survival) and OS (Overall Survival) in patients with advanced urothelial carcinoma treated with pembrolizumab and abraxane; CR (Complete Response) proportion, DOR (Duration of Response) and DOT (Duration of Therapy). • CORRELATIVE: • PD-L1 expression in tumor tissue and TILs at baseline (and in optional tumor biopsy at progression) correlated to response, PFS, OS, DOR, DOT.
	• EXPLORATORY • Development of a Therapy Response Predictor based on baseline immune parameters in tissue. • Quality of Life with patient-reported outcomes (EQ-5D5L) before, during and at end of treatment.

Number of Subjects	36 evaluable subjects
Inclusion Criteria	1. Patients with recurrent unresectable locally advanced or metastatic urothelial carcinoma (aka transitional cell carcinoma). If unresectable locally advanced urothelial cancer: could have been previously radiated, but must have RECIST 1.1 measurable, untreated progression of disease component. 2. Subjects may be either cisplatin-ineligible or platinum-refractory. • Cisplatin ineligibility is defined as meeting at least one of the following criteria: a. Creatinine clearance (calculated or measured) <60 ml/min (but≥ 30mL/min) calculated by Cockcroft-Gault equation (using actual body weight) or by measured 24hour urine collection of creatinine for determination b. Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 audiometric hearing loss c. New York Heart Association Class III/IV heart failure. d. ECOG Performance Status of 2 as determined by treating investigator. • Platinum-refractory is defined as subjects who have progression of disease after receiving platinum-containing chemotherapy (chemotherapy could have been given in the neoadjuvant, adjuvant or metastatic setting). 3. Histological or cytologically proven urothelial carcinoma. Mixed urothelial/non-urothelial cell histologies are allowed but pure non-urothelial cell carcinoma is NOT allowed. 4. Have measurable disease based on RECIST 1.1 as determined by the investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 5. Has urothelial cancer that is not suitable for local therapy administered with curative intent if not already administered. An example of local therapy with curative intent is treatment with chemotherapy and radiation for Stage 3 disease. If unresectable locally advanced urothelial cancer, could have been previously radiated, but must have progression of disease component that is untreated and RECIST 1.1 measurable. 6. Must have recovered (i.e., AE ≤ Grade 1 or stable) from AEs due to a previously administered agent.

	7. ECOG Performance Status of 0, 1 or 2. 8. Prior neoadjuvant or adjuvant systemic therapy or local intravesical chemotherapy or immunotherapy is permitted. 9. Adequate organ function including hematologic, renal and neurologic function (see Section 3.1.9). 10. Women of child-bearing potential (WOCBP-defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must: i. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study medication therapy (including dose interruptions), and for 6 months after last dose of study medication. ii. Have a negative serum or urine pregnancy test (β-hCG) result at screening - this applies even if the subject practices true abstinence* from heterosexual contact. 11. Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following study drug discontinuation, even if he has undergone a successful vasectomy. * True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]. 12. Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE). 13. Be ≥ 18 years of age as of date of signing informed consent. 14. Ability to understand and the willingness to sign a written informed consent.

Exclusion Criteria	1. Prior exposure to immune-mediated therapy, including but not limited to, other anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA 4), anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines is NOT permitted. 2. History of allogenic organ transplantation that requires use of immunosuppressive agents is NOT permitted.

3. Active or prior documented autoimmune or inflammatory disorders are NOT permitted. The following are exceptions to this criterion:

    a) Patients with vitiligo or alopecia.
    b) Patients with hypothyroidism (e.g., following Hashimoto syndrome).
    c) Any chronic autoimmune or inflammatory skin condition that does not require systemic therapy.
    d) Patients without active disease requiring treatment in the last 3 years may be included but only after consultation with principal investigator.
    e) Patients with celiac disease controlled by diet alone may be included but only after consultation with principal investigator.

4. Current or prior use of immunosuppressive medication(s) within 14 days before study treatment is NOT permitted. The following are exceptions to this criterion:

    a) Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
    b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
    c) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

5. Brain metastases or spinal cord compression are NOT permitted unless treated with the patient's condition being stable clinically and radiologically for at least 28 days and off steroids for at least 14 days prior to the start of study treatment. Patients with suspected or known brain metastases at screening should have an MRI (preferred) or CT, preferably with IV contrast, to access baseline disease status.

6. Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) is NOT permitted.

7. Receipt of live attenuated vaccine within 30 days prior to the first study treatment is NOT permitted.

8. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 28 calendar days of the first dose of treatment.

9. Grade $\geq$ 1 peripheral neuropathy (CTCAE criteria) is NOT permitted.

10. If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial therapy.

11. Has a known additional malignancy that is progressing or requires active treatment.

12. Has a history of severe hypersensitivity reaction (e.g., generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to nab-paclitaxel or anti-PD1/PDL1 or human albumin.

	13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. 14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. At the time of signing informed consent is a known regular user (including "recreational use") of any illicit drug(s) or had a recent history (within the last year) of drug or alcohol abuse. 15. Pregnancies: a. Females: nab-paclitaxel can cause harm to an unborn child if given to a pregnant woman. Females may not take part in this study if pregnant or breast-feeding for 6 months after last dose of study drug. Because of the possible risks to an unborn child, women of child-bearing potential (WOBCP) will be asked to take a pregnancy test prior to starting study medication. b. Males: Male subjects should avoid fathering a child while receiving study medication and for 6 months after the last dose of study medication. Males must agree to complete abstinence from heterosexual contact or use a condom during sexual contact with a female of child bearing potential while receiving study medication and within 6 months after last dose of study medication. If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking the product should notify the principal investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. c. Subjects (both males and female) should practice effective contraception during study and for 6 months after the last dose of study medication (Section 3.1.8 i, ii). 16. Patients with biliary obstruction or biliary stent are excluded. 17. Patients with a history of prior thoracic radiation >30 Gy.
Study Product(s), Dose, Route, Regimen	Pembrolizumab 200 mg IV on Day 1 and Abraxane (nab-paclitaxel) 100 mg/m2 IV on Days 1 and 8 in every 21-day cycles.
Duration of Administration	Until disease progression/intolerable toxicity/death. Abraxane may be stopped after 6 cycles per investigator discretion.
Reference Therapy	Pembrolizumab as monotherapy (historical control)
Statistical Methodology	The primary aim of this single-arm phase II trial is to determine the efficacy of the combination of pembrolizumab and abraxane in patients with advanced urothelial carcinoma. The primary endpoint is the ORR (Overall Response Rate = Complete Response + Partial Response per RECIST 1.1) proportion.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

In the United States, bladder cancer is a common malignancy with an estimated 74,690 new cases and 15,580 deaths projected for the year 2014[1]. Although a chemo-sensitive disease initially, the median overall survival of patients with metastatic urothelial carcinoma (UC) treated with first-line cisplatin-based combination chemotherapy is only approximately 15 months [2]. Outcomes for cisplatin-ineligible patients is even more disappointing with median overall survival around 8 months[3]. Hence, patients with advanced UC who are ineligible for cisplatin represent an area of unmet need in urothelial cancer. Platinum-refractory urothelial cancer also continues to be exceedingly lethal disease despite the recent data on activity of checkpoint inhibitor immunotherapy as the response rates are approximately 16-20% only.

Pembrolizumab (also known as MPDL3280A; anti-PDL1) is a blocking monoclonal antibody against anti-PDL1 and PD1 respectively designed to disrupt the interactions of PD1 with PDL1. By inhibiting PDL1-PD1 interaction, such therapies, PDL1 may enable the activation of T cells.

1.1.1 Activity of anti-PD therapy in UC:

Recently, checkpoint inhibitor immunotherapy has been clinically validated in metastatic UC as well in other cancer types[4,5]. The PD-1 receptor-ligand interaction is a major immune checkpoint hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PDL2).

On May 18, 2017, the U.S. Food and Drug Administration granted regular approval to pembrolizumab (KEYTRUDA, Merck and Co., Inc.) for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.

FDA also granted approval to pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. The FDA approval was based on a single-arm trial in 370 patients (KEYNOTE-052) with locally advanced or metastatic urothelial carcinoma who were deemed not eligible for cisplatin-containing chemotherapy.

1.1.2 Activity of anti-PD therapy in cisplatin-ineligible patients with advanced UC – Pembrolizumab

The regular approval for the second-line indication was based on data from Trial KEYNOTE-045, a multicenter, randomized, active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. Patients were randomly assigned (1:1) to receive either pembrolizumab 200 mg every 3 weeks (n=270) or investigator's choice of a chemotherapy regimen (paclitaxel [n=84], docetaxel [n=84], or vinflunine [n=87]) every 3 weeks (n=272). The trial demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) for patients assigned to pembrolizumab as compared to chemotherapy. Median OS was 10.3 and 7.4 months in the pembrolizumab and chemotherapy arms, respectively (HR 0.73; 95% CI: 0.59, 0.91, p=0.004). ORR was 21% for pembrolizumab and 11% for chemotherapy (p=0.002). No statistically significant difference in progression-free survival between the two arms was observed.

The accelerated approval for the first-line indication was based on data from KEYNOTE-052, a single-arm, open-label trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were deemed not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab 200 mg every 3 weeks. With a median follow-up time of 7.8 months, the ORR was 28.6% (95% CI 24, 34) and the median response duration was not reached (range 1.4+, 17.8+ months).

1.1.3 Chemoimmunotherapy:

For many tumors, checkpoint blockade alone has not provided significant benefits or been suboptimal[6,7]. It has been suggested that the immune system could be potentiated with "priming" prior to or in conjunction with an immunotherapy agent[8]. Although numerous chemotherapy agents have known immunosuppressive adverse events, some may possess this "priming" effect to the host immune system, helping to elicit an antitumor T-cell response. Cytotoxic killing of tumors provides a natural source of cancer-associated antigens. Therefore, combining chemotherapy with a checkpoint inhibitor could create an immunogenic "feedback loop", increasing antigen presentation and immune response[8].

In addition to direct cytotoxic killing of tumor cells, standard chemotherapeutic agents can elicit immunogenicity through various mechanisms[8-10]. In brief, many cytotoxic agents have been shown to recruit immune cells (i.e., dendritic cells, macrophages, and natural killer cells) to the tumor microenvironment, enhance tumor-cell death by converting dying tumor cells into endogenous vaccines, stimulate natural killer-dependent antitumor immunity and T-cell responses, induce phagocytosis of cell debris by dendritic cells and antigen presentation to T cells, sensitize tumor cells to cytotoxic T lymphocytes, and disrupt immune suppressor mechanisms by selectively depleting myeloid-derived suppressor cells and suppressing regulatory T cells. These immunomodulatory properties make chemotherapy agents ideal candidates for combination with immunotherapies.

Although high doses of chemotherapy can be immunosuppressive, chemotherapy agents can enhance the antitumor activity of immunotherapy when given at an optimal dose (i.e., lower dose such as weekly regimens)[11-13]. In a preclinical mouse model of relapsed ovarian cancer, a dose dense regimen of low-dose paclitaxel/carboplatin versus the maximum-tolerated-dose regimen was less toxic to the immune system, reduced immunosuppression by components of the tumor microenvironment, and stimulated recruitment of macrophages and CD8+ T cells to tumors[14]. Preclinical evidence also supports giving chemotherapy prior to immunotherapy and at doses slightly higher than the dose levels that begin to induce cytopenias[12]. In a clinical study of patients with metastatic breast cancer, low doses of cyclophosphamide/doxorubicin enhanced the immune response to an allogeneic, HER2-positive, GMCSF-secreting breast-tumor vaccine in patients with breast cancer[15]. In the same study, higher doses of cyclophosphamide were shown to suppress immunity. Therefore, when given at an optimal dose (such as weekly lower doses rather than higher monthly dose), chemotherapy may enhance the immune response rather than suppress it.

1.1.4 Immunomodulatory properties of taxanes:

Taxanes may provide long-term immune benefits, have been shown to increase tumor-infiltrating lymphocytes, and have demonstrated a positive effect on T-cell proliferation and natural killer mediated tumor-cell lysis in breast cancer tumors[16,17]. Paclitaxel may be a particularly strong immune stimulant, as it is able to both activate CD8+ T cells and reduce immunosuppressive cells, such as regulatory T cells[18]. Docetaxel has been shown to increase CD8+ T-cell production RI,)1ÛDVWLPXODWRUIWXPRU-cell killing), but docetaxel does not appear to inhibit the suppressor function of regulatory T cells[19]. In a preclinical model, lower-dose taxanes appeared to induce maturation of myeloid-derived suppressor cells into more mature dendritic cells

independently of TLR4[20]. In patients with advanced breast cancer, treatment with paclitaxel or docetaxel was also associated with enhanced natural killer-cell activity[21]. In addition, a study showed that the antitumor effects of paclitaxel may be mediated by myeloid-derived suppressor cells[22]. Taxanes regulate many aspects of immune function, including lymphocyte recruitment and activation and production of immune-enhancing cytokines, including IL-12, IFNγ, TNFα, and GMCSF, all of which may augment the antitumor activity of immunotherapies[23]. Tumor cell-derived TGFβ has been shown to inhibit paclitaxel-induced macrophage activation; therefore, depletion of TGFβ may provide a mechanism for restoring the immunomodulatory properties of taxanes[24].

1.1.5 Abraxane (nab-paclitaxel): nab-Paclitaxel (ABRAXANE® for Injectable Suspension [Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, Summit, New Jersey, United States; hereafter referred to as "Celgene"], ABI-007) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel in a noncrystalline amorphous state and human albumin with a mean particle size of approximately 130 nanometers. nab-Paclitaxel has been developed to improve the therapeutic index of paclitaxel, also reducing the toxicities associated with Taxol and the CrEL and ethanol vehicle. This may be achieved in part by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor. Because nab-paclitaxel does not contain a solvent vehicle, micellar entrapment observed with Taxol does not occur [25-27]. nabPaclitaxel displays linear pharmacokinetic (PK) characteristics. The novel albumin-bound particle formulation of paclitaxel in nab-paclitaxel conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m2 for nab-paclitaxel (Study DM97-123) versus 175 mg/m2 for Taxol (Nyman, 2004)[28]. The use of albumin-bound paclitaxel also enables nab-paclitaxel to be given in a shorter, more convenient infusion time of 30 - 40 minutes compared with 3 hours to 24 hours with Taxol. Due to its distinct pharmacological and PK properties and therapeutic index, nab-paclitaxel has been approved by regulatory authorities worldwide in over 40 countries/regions as a new product, rather than as a generic formulation of Taxol. nab-Paclitaxel may be given without steroid and anti-histamine premedication, which is required for Taxol to prevent solvent-related HSRs (Taxol US prescribing information). Cremophor EL has been shown to leach plasticizers, specifically di(2-ethylhexyl)phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing [29-34]. Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (e.g., carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol prescribing information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; nonPVC-containing infusion sets (e.g., those with polyethylene lining) should be used (Taxol US prescribing information). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of nab-paclitaxel [25,28].

As of October 2016, nab-paclitaxel is approved under the trade name of ABRAXANE in 65 countries worldwide for the treatment of patients with metastatic breast cancer. ABRAXANE is also approved in 54 countries worldwide for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in 57 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and in Japan for treatment of advanced gastric cancer.

1.1.6 Activity of Abraxane in platinum-refractory UC:

The activity of Abraxane (ABI-007) against platinum-refractory advanced UC was recently described[35]. The multi-institutional phase II study evaluated the efficacy and tolerability of abraxane as a single agent in patients with platinum-refractory metastatic UC. Abraxane was given at 260 mg/m2 IV q3weekly until progression to the 48 patients enrolled. Baseline characteristics included 40 being male; median age of 68 years; ECOG Performance Status 0:1:2 was present in 15:24:8

patients respectively. A median of 5.5 cycles was administered per patient with 17/48 pts (35%) requiring dose reductions. Most frequent adverse events (AE) were alopecia (12%), fatigue (12%), pain (12%), neuropathy (9%) and nausea (4%). The most frequent grade ≥ 3 AEs were pain (45%), hypertension (14%), fatigue (8%), joint stiffness (5%), neuropathy (4%) and weakness (4%). Forty patients are evaluable for response: 1 (2.5%) complete response (CR), 11 (28%) partial responses (PR), 9 (23%) stable disease (SD) and 20 (49%) progressive disease. One patient was inevaluable for response, 7 patients are too early for evaluation. Single agent abraxane was therefore well tolerated with a response rate (CR+PR) of 33% (12/36) and a clinical benefit rate (CR+PR+SD) of 58% (21/36), representing one of the highest reported response rates to date in the second-line UC setting. A NCIC Clinical Trials Group (NCIC CTG) led intergroup trial with the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) comparing abraxane to paclitaxel in platinum-refractory advanced urothelial cancer (NCT02033993) is ongoing.

1.1.7 Taxane-based chemotherapy with immune-checkpoint inhibitors:

Experience with nab-paclitaxel in combination with checkpoint inhibitors are emerging, but early data suggest that nab-paclitaxel-based therapy could augment the antitumor activity of these agents. In a preliminary analysis of a Phase IB trial of patients with various solid tumors, a cohort of 16 efficacy-evaluable patients with advanced NSCLC treated with the combination of atezolizumab (15 mg/kg q3w) plus nab-paclitaxel (100 mg/m2 weekly) plus carboplatin achieved an ORR of 56% and a complete response rate of 25% [36,37]. Two other trial arms of atezolizumab plus either paclitaxel/carboplatin (efficacy evaluable, n=8) or pemetrexed/carboplatin (efficacy evaluable, n=17) also demonstrated favorable ORRs of 50% and 76%, respectively, but no patients receiving the paclitaxel- or pemetrexed-containing regimens have achieved a complete response to date. The most common grade 3 or 4 adverse event was neutropenia (35% in the nab-paclitaxel arm, 29% in the paclitaxel arm, and 25% in the pemetrexed arm). Initial analysis of a cohort of patients with triple-negative breast cancer treated with atezolizumab (800 mg q2w) plus nab-paclitaxel (125 mg/m2 weekly for first 3 of 4 weeks) within the same Phase IB trial demonstrated a best ORR of 71% (42% confirmed) in 24 patients evaluable for efficacy[38]. Patients with metastatic triple-negative breast cancer who received the atezolizumab plus nab-paclitaxel regimen as first-line therapy derived the greatest benefit (best ORR, 46% confirmed). A total of 32 patients with triple-negative breast cancer were evaluable for safety. Neutropenia and decreased neutrophil count were the most common grade 3/4 AE, occurring in 47% of patients receiving atezolizumab plus nab-paclitaxel. The investigators also found that expression of PDL1 was mostly restricted to immune cells in excised tumors, but the level of expression did not appear to correlate with response. Based on the positive results of this Phase IB trial, the combination of atezolizumab and nab-paclitaxel is being evaluated in Phase III trials in triple negative breast cancer and NSCLC.

Interim analysis from a triple negative breast cancer study of a microtubule inhibitor eribulin in combination with pembrolizumab, an anti-PD1 drug, was recently presented at the San Antonio Breast Cancer Symposium 2016[39]. Study 218 is a Phase Ib/II clinical study which examined the activity and safety of eribulin in combination with pembrolizumab in 95 patients with metastatic triple-negative breast cancer previously treated with 0-2 lines of chemotherapy in the metastatic setting. The primary objective of the Phase Ib part was safety and tolerability, and the primary objective of the Phase II part was objective response rate (ORR). At the time of the interim analysis of 39 evaluable patients out of the 89 patients enrolled in the study as of July 2016, ORR was 33.3% (1 patient experienced a complete response and 12 patients experienced a partial response). In addition, the ORR was similar between PD-L1 positive and negative cohorts. Treatment with the PD-L1 inhibitor atezolizumab (MPDL3280A) plus nab-paclitaxel (Abraxane) showed a confirmed objective response rate (ORR) of 66.7% in patients with metastatic triple negative breast cancer (TNBC), according to data presented at the 2015 San Antonio Breast Cancer Symposium[40]. In the phase Ib study, atezolizumab plus nab-paclitaxel was explored across several lines of treatment regardless of PD-L1 status for patients with metastatic TNBC. In the second-line setting, the confirmed ORR was 25% and in the third-line and beyond the ORR

was 28.6%. Across the full trial, the ORR was 41.7%. In the ongoing study, 32 patients received concurrent treatment with nab-paclitaxel at 125 mg/m2 and atezolizumab at 800 mg. In the initial safety cohort of the study (n = 8), atezolizumab was administered on days 1 and 15 along with nab-paclitaxel on days 1, 8, and 15 in a 28-day cycle. In a serial biopsy cohort, 24 patients received nab-paclitaxel on days 1 and 8 for the first cycle followed by concurrent treatment with both agents using the safety cohort schedule. In the serial biopsy arm, a pretreatment biopsy was taken ≥ 7 days before the first cycle. Additional biopsies were obtained between days 10 and 15 during the first cycle then again 4 weeks after the first dose of atezolizumab. Responses were confirmed if seen on two or more sequential scans. The primary endpoint of the study was safety, with key secondary endpoints focused on ORR, duration of response, progression-free survival, and biomarker analyses. The median age of patients in the study was 55.5 years, and most had an ECOG PS of 0 (19%) or 1 (81%). The number of prior systemic therapies received was 5, although a group of patients were enrolled in the frontline setting (n = 9). Prior to entering the study, 87% of patients had received a taxane. At the time of the data cutoff, 24 patients with a minimum follow-up of ≥ 3 months were evaluable for efficacy. Across all groups, when considering unconfirmed responses, the ORR was 70.8%, which included a complete response rate of 4.2%. Additionally, the stable disease rate was 20.8%, for an overall disease control rate of 91.6%. At the time of the analysis, 11 of 17 responses (65%) remained ongoing.

1.2 Rationale

Given the dire unmet clinical need to improve outcomes for patients who are cisplatin ineligible as well as those who are platinum-refractory in advanced urothelial cancer, the preliminary evidence of robust activity of abraxane in advanced urothelial cancer, the proven activity of pembrolizumab in both platinum-refractory and cisplatin-ineligible patients with advanced urothelial cancer, and the emerging data from ongoing studies showing excellent tolerance and promising combinatorial activity of the two agents when combined in other cancer types including potential synergy between the two agents, **we hypothesize that the addition of abraxane to pembrolizumab in advanced urothelial cancer would augment the anti-cancer immune response to pembrolizumab and result in greater clinical efficacy and benefit to patients from both agents in a synergistic manner**.

We therefore propose a single arm phase 2 study of abraxane in combination with pembrolizumab in cisplatin ineligible as well as platinum-refractory patients with advanced urothelial cancer (metastatic or locally advanced unresectable).

Rationale for reduction in starting dose of abraxane: Experience in the first 17 subjects enrolled revealed: Grade ≥3 adverse events (AE) occurred in 15/17 pts including fatigue (n=5), peripheral neuropathy (n=3), anemia (n=3), and oral mucositis (n=3). Five pts discontinued treatment due to AEs, all attributed to abraxane. Hence, we believe a dose reduction in starting dose of abraxane to 100 mg/m2/dose down from 125 mg/m2/dose is appropriate.

1.3 Correlative Studies[41]

PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression on tumor cells is associated with a poor prognosis in patients with UBC [41, 42]. Tumor tissue will be archived for future testing including PD-L1 status by IHC.

In the IM vigor 210 trial of atezolizumab in urothelial cancer, PD-L1 expression on immune cells infiltrating tumor tissue did correlate with response. Twenty-six percent of patients whose tumor immune cells were highly positive by IHC responded whereas only 8% of patients whose tumor

immune cells were PDL1 negative had a response. While displaying an important trend, PD-L1 expression is not an optimal discriminatory biomarker by itself, as evidenced by the fact that 2% of patients in the PD-L1 negative group did have a complete response to atezolizumab. Data for pembrolizumab PD-L1 is similar[5].

We would like to correlate response with PD-L1 status in patients treated with abraxane and pembrolizumab. We plan to test for PD-L1 expression with the corresponding PD-L1 IHC 22C3 pharmDx assay per the commercial assay specifications in the future after trial accrual is complete.

2.0 STUDY OBJECTIVES

2.1 OBJECTIVES:

PRIMARY:

- To determine the efficacy of abraxane and pembrolizumab antibody in advanced urothelial cancer.

SECONDARY:

- To assess the safety and toxicity of abraxane and pembrolizumab antibody in patients with advanced urothelial cancer.

- To estimate secondary measures of efficacy with abraxane and pembrolizumab antibody in advanced urothelial cancer.

EXPLORATORY/CORRELATIVE:

- To correlate PD-L1 expression on tumor cells and TILs in baseline archival tumor tissue with primary and secondary efficacy measures.

- To develop a therapy response predictor based on immune parameters in tumor tissue and blood.

- To determine the quality of life of patients enrolled on the study as reflected in patient reported outcomes.

2.2 ENDPOINTS:

PRIMARY:

- ORR (Overall Response Rate) proportion in patients with advanced urothelial carcinoma treated with pembrolizumab and abraxane.

SECONDARY:

- Safety and Toxicity of the combination in patients with advanced urothelial carcinoma.

- PFS (Progression-Free Survival), OS (Overall Survival), CR (Complete Response) proportion, DOR (Duration of Response) and DOT (Duration of Therapy) in patients with advanced urothelial carcinoma treated with abraxane and pembrolizumab.

EXPLORATORY/CORRELATIVE:

- Future testing of PD-L1 expression in tumor tissue and TILs at baseline (and in optional tumor biopsy at progression) correlated to objective response, PFS, OS, DOR, DOT.

- Development of a Therapy Response Predictor based on immune parameters in tumor tissue and blood.

- Quality of Life with patient-reported outcomes (EQ-5D-5L) before, during and at end of treatment.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

3.1.1 Patients with recurrent unresectable locally advanced or metastatic urothelial carcinoma (aka transitional cell carcinoma).

If unresectable locally advanced urothelial cancer, could have been previously radiated, but must have RECIST 1.1 measurable, untreated progression of disease component.

3.1.2 Subjects may be either cisplatin-ineligible or platinum-refractory.

- Cisplatin ineligibility is defined as meeting at least one of the following criteria:

  a. Creatinine clearance (calculated or measured) <60 ml/min (but≥ 30mL/min) calculated by Cockcroft-Gault equation (using actual body weight) or by measured 24-hour urine collection of creatinine for determination
  b. Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 audiometric hearing loss
  c. New York Heart Association Class III/IV heart failure.
  d. ECOG Performance Status of 2 as determined by treating investigator.

- Platinum-refractory is defined as subjects who have progression of disease after receiving platinum-containing chemotherapy (chemotherapy could have been given in the neoadjuvant, adjuvant or metastatic setting).

3.1.3 Histological or cytologically proven urothelial carcinoma. Mixed urothelial/non-urothelial cell histologies are allowed but pure non-urothelial cell carcinoma is NOT allowed.

3.1.4 Have measurable disease based on RECIST 1.1 as determined by the investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

3.1.5 Has urothelial cancer that is not suitable for local therapy administered with curative intent if not already administered. An example of local therapy with curative intent is treatment with chemotherapy and radiation for Stage 3 disease.

If unresectable locally advanced urothelial cancer, could have been previously radiated, but must have progression of disease component that is untreated and RECIST 1.1 measurable.

3.1.6 Must have recovered (i.e., AE ≤Grade 1 or stable) from AEs due to a previously administered agent.

3.1.7 ECOG Performance Status of 0, 1 or 2.

3.1.8 Prior neoadjuvant or adjuvant systemic therapy or local intravesical chemotherapy or immunotherapy is permitted.

3.1.9 Adequate organ and marrow function as defined below:

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥1500/mm3
Hemoglobin (Hgb)	≥9 g/dL with or without pRBC transfusion
Platelets (Plt)	≥ 100,000/mm^3
Renal	
Calculated or measured creatinine clearance	≥30 mL/min calculated by Cockcroft-Gault equation (using actual body weight) or by measured 24-hour urine collection of creatinine for determination.
Hepatic	
Bilirubin	≤1.5 x upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≤2.5 x ULN
Alanine aminotransferase (ALT)	≤2.5 x ULN
Total Bilirubin	≤1.5 x ULN

3.1.10 Women of child-bearing potential (WOCBP-defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:

i. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study medication therapy (including dose interruptions), and for 6 months after last dose of study medication.
ii. Have a negative serum or urine pregnancy test (β-hCG) result at screening this applies even if the subject practices true abstinence* from heterosexual contact.

3.1.11 Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while

participating in the study, during dose interruptions and for 6 months following study drug discontinuation, even if he has undergone a successful vasectomy.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

3.1.12 Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE).

3.1.13 Be ≥ 18 years of age as of date of signing informed consent.

3.1.14 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Prior exposure to immune-mediated therapy, including but not limited to, other anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA 4), anti-PD1, anti –PDL1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines is NOT permitted.

3.2.2 History of allogenic organ transplantation that requires ongoing use of immunosuppressive agents is NOT permitted.

3.2.3 Active or prior documented autoimmune or inflammatory disorders are NOT permitted. The following are EXCEPTIONS to this criterion and are allowed:

a. Patients with vitiligo or alopecia, Type I diabetes mellitus.
b. Patients with hypothyroidism (e.g., following Hashimoto syndrome).
c. Any chronic autoimmune or inflammatory skin condition that does not require systemic therapy.
d. Patients without active disease requiring treatment in the last 3 years may be included but only after consultation with principal investigator.
e. Patients with celiac disease controlled by diet alone may be included but only after consultation with principal investigator.

3.2.4 Current or prior use of immunosuppressive medication(s) within 14 days before study treatment is NOT permitted. The following are EXCEPTIONS to this criterion and are allowed:

a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

3.2.5 Brain metastases or spinal cord compression are NOT permitted unless they have been treated with the patient's condition being stable clinically and radiologically for at least 28 calendar days and off steroids for at least 14 calendar days prior to the start of study treatment. Patients with suspected or known brain metastases at screening should have an MRI (preferred) or CT brain/head, preferably with IV contrast, to assess baseline disease status.

3.2.6 Active infection requiring systemic therapy including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) is NOT permitted.

3.2.7 Receipt of live attenuated vaccine within 28 calendar days prior to the first study treatment is NOT permitted.

3.2.8 Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 28 calendar days of the first dose of treatment.

3.2.9 CTCAE Grade $\geq$ 1 peripheral neuropathy is NOT permitted.

3.2.10 If subjects received major surgery they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial therapy.

3.2.11 Has a known additional malignancy that is progressing or requires active treatment.

3.2.12 Has a history of severe hypersensitivity reaction (e.g., generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to nab paclitaxel or anti-PD1/PDL1 or human albumin.

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

3.2.14 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. At the time of signing informed consent is a known regular user (including "recreational use") of any illicit drug(s) or had a recent history (within the last year) of drug or alcohol abuse.

3.2.15 Pregnancies

a. Females: *nab*-paclitaxel can cause harm to an unborn child if given to a pregnant woman. Females may not take part in this study if pregnant or breast-feeding for 6 months after last dose of study drug. Because of the possible risks to an unborn child, women of child-bearing potential (WOBCP) will be asked to take a pregnancy test prior to starting study medication.

b. Males: Male subjects should avoid fathering a child while receiving study medication and for 6 months after the last dose of study medication. Males must agree to complete abstinence from heterosexual contact or use a condom during sexual contact with a female of child bearing potential while receiving study medication and within 6 months after last dose of study medication. If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking the product should notify the principal investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

c. Subjects (both males and female) should practice effective contraception during study and for 6 months after the last dose of study medication (Section 3.1.8 i, ii).

3.2.16 Patients with biliary obstruction or biliary stent are excluded.

3.2.17 Patients with a history of prior thoracic radiation >30 Gy.

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed by the Oncology Clinical Trials Support Unit (OCTSU). The patient will not be considered registered and enrolled in the study until all information is confirmed by the OCTSU Data Manager.

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be assigned a Patient Study ID number and documented on a Screening and Enrollment Log.

It is the responsibility of the principal investigator to determine patient eligibility prior to submitting patient registration request to the OCTSU. The eligibility worksheet and all pertinent source documents will be maintained in the patient's chart.

Patients found to be ineligible for participation after being consented will be considered screen failures and documented as such in the Screening and Enrollment Log.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 business days of enrollment to the study.

5.1.1

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Starting Dose**	**Route**	**Schedule**	**Cycle Length**
Abraxane (nab paclitaxel)	Prochlorperazine 10 mg once oral/IV if unable to tolerate oral route	100 mg/m^2/dose	IV over 30-40 minutes	Days 1, 8	21 days
Pembrolizumab	None mandated	200 mg/dose	IV over 60 minutes (+/-5 minutes). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.	Day 1	

- **Administer abraxane first followed by pembrolizumab.**
- **Abraxane infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose**.
- **Abraxane can be discontinued after 6 cycles at investigator discretion, or for intolerable toxicities and pembrolizumab alone could be continued**.
- **Abraxane alone can be continued if pembrolizumab is stopped for pembrolizumab related toxicities, and vice versa**.

5.1.2 Dose levels

Dose level	Pembrolizumab Dose	Abraxane Dosing
0	200 mg	100 mg/m^2
-1	200 mg	75 mg/m^2
-2	200 mg	50 mg/m^2

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

5.2.1 Hematological Toxicities (only applicable to abraxane dosing)

Hematological Toxicity Dose Reductions for Abraxane		
ANC[1]	**Platelets**	**Action**
•PL or	>100,000/PL	None.

1000-1499/PL or	75,000-99,000/PL	*-1st Occurrence:* Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at TBD dose. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at 1 dose level lower if possible. If no lower dose level possible, stop abraxane. *-3rd Occurrence:* Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at 1 dose level lower if possible. If no lower dose level possible, stop abraxane. *-4th Occurrence*: Discontinue abraxane
500-999/PL or	50,000-74,000/PL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at 1 dose level lower if possible. If no lower dose level possible, stop abraxane. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Do not replace missed doses. Restart next treatment at 1 dose level lower if possible. If no lower dose level possible, stop abraxane. *-3rd Occurrence*: Discontinue abraxane.
<500/PL or	<50,000/PL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/µL and platelets ≥ 100,000/µL. Restart next treatment at 1 dose level lower if possible. If no lower dose level possible, stop abraxane. *-2nd Occurrence*: Discontinue abraxane.
[1]Note: G-CSF (Filgrastim) may be added for low ANC on day of treatment *BEFORE* a dose reduction is instituted at treating physician's discretions. Neulasta® on day 9 of a cycle is allowed if preferred.		

5.2.2 Non-hematological Toxicities (except neuropathy) Dosing level changes

NCI CTCAE Grade	Pembrolizumab	Abraxane (nab-paclitaxel)

1	Please see Section 5.2.4	No change from original starting dose
2	Please see Section 5.2.4	Hold until improved to ≤ Grade 1, then reduce abraxane by 1 dose level when resuming. If no lower dose level possible, stop abraxane.
3	Please see Section 5.2.4	Hold until improved to ≤ Grade 1, then reduce abraxane by 1 dose level when resuming. If no lower dose level possible, stop abraxane.
Second or greater episode of grade 3 or 1st or greater episode of grade 4 toxicity	Please see Section 5.2.4	Discontinue abraxane.

For Abraxane induced neuropathy as a special event:
Grade 1: Dose reduce abraxane by -1 level and continue; recommend adding gabapentin or pregabalin
Grade 2: Hold abraxane till grade 1 or less; then dose reduce abraxane by -1 level and resume; recommend adding gabapentin or pregabalin
Grade 3: Discontinue abraxane permanently; recommend adding gabapentin or pregabalin
Grade 4: Discontinue abraxane permanently; recommend adding gabapentin or pregabalin

N.B.: Can continue pembrolizumab if abraxane is held or discontinued.

N.B.: If abraxane is held or discontinued, can cancel day 8 visit along with associated labs/procedures and infusion.

5.2.3 Recommendations for Dose of Abraxane on C1 D8 and beyond in Patients with Hepatic Impairment.

	SGOT (AST) OR SGPT (ALT) Levels		Bilirubin Levels	ABRAXANE Dose
Mild	< 10 x ULN	AND	>ULN to ≤ 1.5 x ULN	100 mg/m^2
Moderate	< 10 x ULN	AND	>1.5 to ≤ 2.5 x ULN	HOLD
Severe	< 10 x ULN	AND	>3 to ≤ 5 x ULN	HOLD
	< 10 x ULN	OR	>5 x ULN	HOLD

5.2.4 Dosing delays and holds for Pembrolizumab:

- No dose delays for pembrolizumab are needed for hematologic changes.
- Doses that are held will be skipped, not made up later.
- With any grade 2 or higher **non-hematologic toxicity deemed to be related to pembrolizumab**, hold pembrolizumab and refer to section 5.2.1. If adverse event is not an event of interest and improves to grade 1 or better, pembrolizumab may be resumed.
- If non-hematologic toxicity does not improve to grade 1 or better in 12 weeks from prior dose, discontinue pembrolizumab.
- Infusion-Related Reaction: Pembrolizumab can cause severe or life-threatening infusion related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving pembrolizumab. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue Pembrolizumab.

Certain adverse events that are possibly immune mediated warrant special monitoring and management and are outline below to guide investigators.

5.2.4.1 Pulmonary:

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

Grade of pneumonitis (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 Radiographic Changes Only	• Consider delay of pembrolizumab • Monitor for symptoms every 2-3 days • Consider pulmonary and infectious disease consultations	• Re-image at least every 3 weeks • If worsening, treat as grade 2, 3 or 4

Grade 2
Mild to moderate new symptoms
	• Delay pembrolizumab
	• Consult pulmonary and infectious disease
	• Monitor symptoms daily, consider hospitalization
	• 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent
	• Consider bronchoscopy and/or lung biopsy
		• Re-image every 1-3 days
		• Consider prophylactic antibiotics while on steroids
		• If improves:
		  • When symptoms return to near baseline, taper steroids over at least one month
		  • When steroids are at 10mg oral prednisone (or equivalent) or below, resume pembrolizumab
		  • If not improving after 2 weeks or

		worsening, treat as grade 3 or 4
Grade 3 or 4 Severe new symptoms and/or new or worsening hypoxia	• Discontinue pembrolizumab • Hospitalize • Consult pulmonary and infectious disease • 1-2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections like PCP/PJP • Consider bronchoscopy and/or lung biopsy	• If improves to baseline: • Taper steroids over 4 weeks • If not improving after 48 hours or worsening Add additional immunosuppressive agent(s) (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin or mycophenolate mofetil)

5.2.4.2 Gastrointestinal:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Opiates or narcotics may mask symptoms of perforation. Infliximab should not be used in case of perforation or sepsis.

Grade of diarrhea/colitis (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 • Diarrhea of less than 4 stools per day over baseline or asymptomatic colitis	• Continue pembrolizumab • Symptomatic treatment such as loperamide	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately • If worsening, treat as grade 2,3 or 4
Grade 2 • Diarrhea of 4-6 stools per day	• Hold pembrolizumab and start symptomatic treatment such as loperamide	• If improves to grade 1, resume pembrolizumab o Resume pembrolizumab if the event improves to

over baseline OR • IV fluids needed < 24 hours due to diarrhea OR • Colitis with abdominal pain or blood in stool	○ 1-2 mg/kg per day of oral prednisone or equivalent ○ Consider prophylactic antibiotics for opportunistic infections like PCP	grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10mg oral prednisone per day ○ When symptoms improve to grade 1, taper steroids over at least one month • If worsening, treat as grade 3 or 4
Grade 3 • Diarrhea ≥ 7 stools per day over baseline OR • IV fluids needed for ≥ 24 hours due to diarrhea OR • Colitis with severe abdominal pain or medical intervention indicated	• Delay pembrolizumab • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Start prophylactic antibiotics for opportunistic infections such as PCP • Consider lower endoscopy	• If improves • Continue steroids until symptoms are grade 1, then taper over at least one month • Resume pembrolizumab if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10mg oral prednisone per day • If persists for >3-5 days or recurs after improvement, add infliximab 5mg/kg if no contraindication (Note: infliximab should not be used in cases of perforation or sepsis)
Grade 4 Life threatening or perforation	• Discontinue pembrolizumab • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Start prophylactic antibiotics for opportunistic infections such as PCP • Consider lower endoscopy	• If improves • Continue steroids until symptoms are grade 1, then taper over at least one month • If persists for >3-5 days or recurs after improvement, add infliximab 5mg/kg if no contraindication (Note: infliximab should not be used in cases of perforation or sepsis)

5.2.4.3 Endocrinopathy:

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy. Consider visual field testing, endocrinology consultation and imaging.

Endocrinopathy	Management	Follow-up

Asymptomatic thyroid-stimulating hormone (TSH) elevation	• Continue pembrolizumab • If TSH <0.5 x LLN or TSH >2x ULN, or consistently out of range in subsequent measurements, include free T4 in subsequent measurements as clinically indicated • Consider endocrinology consult	
Symptomatic Hypothyroidism	• Initiate thyroid replacement	
Symptomatic Hyperthyroidism	• Delay pembrolizumab • Consider endocrinology consult • Initiate anti-thyroid drug	• Resume pembrolizumab when symptoms of hyperthyroidism are controlled and thyroid function is improving
Hypophysitis	• Administer corticosteroids and hormone replacement as clinically indicated • Delay pembrolizumab for grade 2 or 3 hypophysitis • Permanently discontinue pembrolizumab for grade 4 hypophysitis	
Symptomatic Adrenal Insufficiency	• Delay Pembrolizumab • Administer methylprednisolone 1-2 mg/kg/day IV followed by oral prednisone 1-2mg/kg per day or equivalent once symptoms improve • Add prophylactic antibiotics for opportunistic infections	• If improves to ≤ grade 1, taper steroids over at least one month • Resume pembrolizumab if the event improves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤10 mg oral prednisone per day and the patient is on stable replacement therapy if required

5.2.4.4 Hepatic:

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

Grade of Liver Test Elevation (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 AST or ALT >ULN to 3x ULN and/or total	• Continue pembrolizumab	• Continue liver function test monitoring per protocol • If worsening, treat as grade 2,3, or 4

bilirubin >ULN to 1.5x ULN		
Grade 2 AST or ALT >ULN to 3-5x ULN and/or total bilirubin >ULN to 1.5-3x ULN	• Delay pembrolizumab • Administer corticosteroids at a dose of 0.51mg/kg/day oral prednisone	• Resume pembrolizumab if returns to baseline • If persists >5-7 days or worsens, treat as grade 3 or 4
Grade 3 or 4 AST or ALT >5x ULN and/or total bilirubin >3x ULN	• Discontinue pembrolizumab • Increase frequency of monitoring to every 1-2 days • 1-2mg/kg/day methylprednisolone IV or IV equivalent for grade 3 and 2 mg/kg/day methylprednisolone IV for grade 4 • Add prophylactic antibiotics for opportunistic infections like PCP • Consult gastroenterologist	• If improves to grade 2, taper steroids over at least one month • If does not improve within 3-5 days or worsens after improvement: o Add mycophenolate mofetil 1g twice daily o If no response within an additional 3-5 days, consider other immunosuppressive agents per local guidelines

5.2.4.5 Pancreatic/Renal:

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

Grade of pancreatic toxicity (NCI CTCAE v4.03)	Management	Follow-up
Grade 1-2 Amylase or Lipase up to 2x ULN	• Continue pembrolizumab	

Grade 2 or 3 Pancreatitis or Grade 3 serum amylase or lipase level (>2x ULN)	• Delay pembrolizumab • Treat with 1-2mg/kg IV methylprednisolone or equivalent per day	• Once symptoms improve, follow with 1-2mg/kg of oral prednisone or equivalent per day • Resume pembrolizumab if amylase/lipase improves to ≤ grade 1 within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
Grade 4 or recurrent pancreatitis	• Discontinue pembrolizumab • Treat with 1-2mg/kg IV methylprednisolone or equivalent per day	• Once symptoms improve, follow with 1-2mg/kg of oral prednisone or equivalent per day and taper for ≥ 1 month

5.2.4.6 Neurological:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy.

Grade of neurological toxicity (NCI CTCAE v 4.03)	Management	Follow-up
Grade 1 • Asymptomatic or mild symptoms • Intervention not indicated	• Continue pembrolizumab	• Continue to monitor the patient, if worsening treat as grade 2, 3, or 4
Grade 2 • Moderate symptoms • Limiting instrumental ADLs	• Delay pembrolizumab • Treat symptoms per institutional guidelines • Consider 0.5-1mg/kg per day methylprednisolone IV or oral equivalent	• If returns to baseline, resume pembrolizumab • If worsens, treat as grade 3 or 4
Grade 3 or 4 • Severe symptoms • Limiting self-care ADLs	• Discontinue pembrolizumab • Consult Neurology • Treat symptoms per institutional guidelines • 1-2mg/kg per day IV methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections	• If improves to grade 2, taper steroids over at least one month • If worsens, consider IVIG or other immunosuppressive therapies per institutional guidelines
Meningitis or Encephalitis	• Discontinue pembrolizumab • 1-2mg/kg per day IV methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections	• If improves, convert to oral steroids (prednisone 60mg/day or equivalent) • When symptoms improve to ≤ grade

		1, taper steroids over at least one month

5.2.4.7 Skin:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of Rash (NCI CTCAE v4.03)	Management	Follow-up
Grade 1-2 Covering ≤ 30% body surface area (BSA)	• Symptomatic therapy (such as antihistamines, topical steroids) • Continue pembrolizumab	• If persists 1-2 weeks or recurs ○ Consider skin biopsy • Delay pembrolizumab ○ Consider 0.5-1mg/kg/day methylprednisolone IV or oral equivalent ○ Once improving, taper steroids for at least one month ○ Consider prophylactic antibiotics for opportunistic infections like PCP/PJP ○ Resume pembrolizumab if rash improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day • If worsens, treat as grade 3 or 4
Grade 3-4 Covering >30% BSA or life threatening consequences	• Delay or discontinue pembrolizumab. If SJS or TEN, permanently discontinue pembrolizumab. • Consider skin biopsy • Consult dermatology • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	• If improves to grade 1: ○ Taper steroids over at least one month ○ Resume pembrolizumab if rash improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day

If Steven Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) develops, permanently discontinue Pembrolizumab.

5.2.4.8 Renal:
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue protocol therapy

Grade of elevation in serum creatinine (NCI CTCAE v4.03)	Management	Follow-up
Grade 1 Serum creatinine >ULN and >baseline but ≤1.5x baseline	• Continue pembrolizumab • Monitor serum creatinine weekly	• If returns to baseline, resume creatinine monitoring per protocol • If worsens, treat as grade 2, 3, or 4
Grade 2 Serum creatinine ≤ 6 x ULN	• Delay or discontinue pembrolizumab • Monitor serum creatinine every 2-3 days • 1-2 mg/kg/day methylprednisolone IV or oral equivalent • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy	• If improves to grade 1 o Taper steroids over at least one month o Resume pembrolizumab if improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day • If elevation persists >7 days or worsens, treat as grade 4
Grade 3 or 4 Serum creatinine > 6x ULN	• Discontinue pembrolizumab • Monitor serum creatinine daily • 1-2mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consult nephrology • Consider renal biopsy	• If improves to grade 1 o Taper steroids over at least one month o Resume pembrolizumab if improves to ≤ grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day

5.3 Concomitant Medications/Treatments

Systemic corticosteroids greater than the equivalent of 10 mg of prednisone or equivalent alternative steroid (except physiologic dose for adrenal replacement therapy) or other immunosuppressive agents (such as cyclosporine or methotrexate) and any other medications that could potentially impact the efficacy or safety of the study as judged by the treating investigator are NOT permitted from time of registration to subjects completing protocol therapy unless clinically indicated to manage adverse events or life threatening or serious conditions as determined by the treating investigator.

Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4.

5.4 Other Modalities or Procedures

Pembrolizumab should be held (no specified time period, at discretion of treating investigator) for any surgery until subject is judged to be stable to resume by treating

investigator as adequate information does not exist on its effects on wound healing. When resumed, same dose level will be maintained.

Abraxane should be held (no specified time period, at discretion of treating investigator) for any surgery until subject is judged to be stable to resume by treating investigator. When resumed, same dose level will be maintained.

Percutaneous procedures like imaging guided biopsies and central line placements do not require pembrolizumab or abraxane to be necessarily held unless treating investigator judges it may increase risk of complications.

5.5 Duration of Therapy

Treatment may continue until one of the following criteria apply:

- Disease progression by RECIST1.1 as defined in Section 7.1.4. Subject may be continued on same regimen beyond one objective progression by RECIST 1.1 if clinically stable at the discretion of treating investigator and with the permission of the principal investigator.
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.5 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7 and in section 6.0. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (Section 5.8).

5.7 Duration of Follow-Up

Patients will be followed for up to 24 months after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed with a phone call or clinic visit until resolution or stabilization of the adverse events.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

5.8.1 Patient withdraws consent (termination of treatment and follow-up);
5.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
5.8.3 Patient is unable to comply with protocol requirements;
5.8.4 Treating physician determines continuation on the study would not be in the patient's best interest;

5.8.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.8.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.8.7 Lost to Follow-up.
5.8.8 Termination of the study by The University of Michigan;
5.8.9 Patient completes protocol treatment and follow-up criteria.

5.9 Patient Replacement

Patients who do not receive any dose of the study drug will be replaced.

6.0 STUDY PROCEDURES

6.1 SCHEDULE OF ASSESSMENTS:

1 cycle (C) = 21 days (D)

Assessment	Screening	C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C3 D8	Subsequent Cycles as per C1 (duration of therapy per section 5.5, 5.6, 5.8)	EOT	Follow-up every 12 weeks[8] +/- 7 business days for 24 months/death
Informed Consent	X									
Tumor tissue specimen identified (15 FFPE unstained slides required; blocks preferred)	X									
Whole blood, Plasma, serum for banking	X									
History, PE, Concomitant Meds, Weight, Vital Signs[1]	X	X		X		X		X (Day 1 only)	X	
ECOG Performance Status	X	X		X		X		X (Day 1 only)	X	
QoL (EQ-5D-5L)	X			X		X		X	X	
Toxicity Evaluation	X	X		X		X		X (Day 1 only)	X	
Pregnancy Test for WOBCP, HIV, HBV, HCV serology [2]	X									
CBC with diff and plat [3]	X	X	X	X	X	X	X	X	X	
COMP [4]	X	X	X	X	X	X	X	X	X	
TSH, free T3, free T4 (IF Clinically Indicated: FSH, LH, ACTH)	X					X		X_6	X	
Amylase, Lipase	X					X		X_6	X	
Tumor response assessment (CT chest, CT or MRI abdomen/pelvis; CT or MRI brain if indicated) [5]	X					X		X_5		X
Optional Tumor Biopsy									X_7	
Pembrolizumab		X		X		X		X (D1)		
Abraxane		X	X	X	X	X	X	X (D1, 8)		

1. Vital signs will include temperature, pulse, respirations, blood pressure; height will be obtained at screening only.
2. WOCBP: Women of child bearing potential; urine or serum pregnancy test.
3. CBC with diff includes total WBC, hemoglobin, hematocrit and differential of the WBC including absolute counts. D15 CBC checks are at discretion of treating investigator.
4. COMP or Comprehensive metabolic profile includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin.

5. With or without intravenous contrast, before or on associated visit. CT or MRI brain with (preferred) or without IV contrast if suspected or known brain metastases. Frequency of tumor assessments will be q2 cycles (i.e. q 6 weeks) for first 4 assessments beyond baseline and then q 3 cycles (i.e. 9 weeks) subsequently. If CR/PD, should be confirmed with repeat imaging after an interval of at least 4 weeks.
6. Every 42 calendar days ± 7 business days.
7. Optional tissue biopsy collection if subject consents; +/- 14 working days.
8. Follow up with phone call or with clinic visit.

NOTE:
All assessments have a window of ± 3 business days unless otherwise mentioned.

G-CSF (Filgrastim) may be added for low ANC on day of treatment *BEFORE* a dose reduction is instituted at treating physician's discretion. Neulasta® on day 9 of a cycle is allowed if preferred.

An Optional Tumor Biopsy would be performed, if subject has been consented to it, at progression.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.1 Definitions

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

Response Evaluable Population for primary endpoint: Only those patients who have had their disease re-evaluated by imaging after 2 cycles of therapy OR exhibit objective or unequivocal clinical disease progression prior to the end of cycle 2 will be considered evaluable for the primary endpoint. These patients will have their response classified according to the definitions stated below.

7.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be

accurately measured with calipers should be recorded as non-measurable)

- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered may be defined in the protocol when appropriate.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should

be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

7.1.3 Guidelines for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

7.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

8.0 ADVERSE EVENTS

For the most recent safety update, please refer to the current package inserts for nab-paclitaxel and pembrolizumab.

Overdose

Overdose, as defined for this protocol, refers to ABRAXANE®, combination products and comparator dosing only.

On a per dose basis, an overdose is defined as 10% over the protocol-specified dose of Abraxane® assigned to a given patient, regardless of any associated adverse events or sequelae.

IV

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, **therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.**

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 60 days are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The principal investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the principal investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the principal investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the principal investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration or intervention through 30 days after the last dose of study treatment or study intervention. Any serious adverse event that occurs more than 30 days after the last study treatment or intervention and is considered related to the study treatment or intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment or intervention for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration or intervention is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.2, occurring from the initial study treatment administration or intervention through 30 days following the last dose of the study treatment or study intervention must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment or intervention is also considered an adverse event.

8.2 Definitions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

- Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.

8.2.2 Serious Adverse Event

An adverse event is considered “serious” if, in the view of the principal investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered ‘life-threatening’ if, in the view of either the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of “Serious Adverse Event”. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.2.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.2.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.3.2 Attribution of the AE

The principal investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study [treatment/intervention].
Probable – The AE *is likely related* to the study [treatment/intervention].
Possible – The AE *may be related* to the study [treatment/intervention].
Unlikely – The AE *is doubtfully related* to the study [treatment/intervention].
Unrelated – The AE *is clearly NOT related* to the study [treatment/intervention].

8.4 Serious Adverse Event Reporting Guidelines

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the principal investigator within 2 business days of study team's knowledge of any event meeting the criteria and definition of a

serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment.

The investigator must report all events meeting the criteria and definition of a serious adverse events that are unexpected and possibly related (definite, probable or possible) to study treatment to the local IRB within 7 days of study team's knowledge.

All Serious Adverse Events that are unexpected and possibly related (definite, probable or possible) to study treatment will be reported to the IRB using the MEDWATCH 3500A form.

Principal Investigator Contact Information for SAE reporting:

Ajjai Alva, MD
Hematology/Oncology
University of Michigan
7316 Cancer Center
1500 E. Medical Center Drive
Ann Arbor, MI 48109

Phone: (734) 936-0091
Fax: (734) 615-2719
Email: ajjai@umich.edu

8.5 Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-BLD-12813- PI-Alva) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to ABRAXANE® based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet

the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Adverse event updates/IND safety reports
Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE suspected of being related to the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file, including correspondence with Celgene and the IRB/EC.

8.6 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 7 calendar days of the study team becoming aware of the problem.

8.8 Reference Safety Information: Treatment-Emergent Adverse Drug Reactions Reported with *nab*-Paclitaxel

System Organ Class MedDRA Preferred Term	Frequency – CIOMS IV WG Criteria[a]	Serious[b]	Severity Life Threatening	Severity Death	New LPT[d]
Blood and lymphatic system disorders					
Anemia	Very common	X			
Bone marrow depression	Uncommon	X			
Febrile neutropenia	Common	X			
Leukopenia	Very common	X			
Lymphopenia	Common	X			
Neutropenia	Very common	X			
Pancytopenia	Common	X			
Thrombocytopenia	Very common	X			
Thrombotic thrombocytopenic purpura	Uncommon	X			
Cardiac disorders					
Arrhythmia	Uncommon	X		X	
Atrioventricular block	Rare	X			
Cardiac arrest	Uncommon	X		X	
Cardiac failure congestive	Common	X		X	
Left ventricular dysfunction	Uncommon	X			
Palpitations	Common	X			
Sinus bradycardia	Uncommon	X			
Supraventricular tachycardia	Uncommon	X			
Tachycardia	Common	X			
Eye disorders					
Conjunctivitis	Uncommon				
Cystoid macular edema	Uncommon	X			

Lacrimation increased	Common				
Keratitis	Uncommon	X			
Maculopathy	Uncommon	X			
Visual impairment	Common	X			
Gastrointestinal disorders					
Abdominal pain	Very common	X			
Colitis	Common	X			
Constipation	Very common	X			
Diarrhea	Very common	X			
Dry mouth	Common	X			
Dyspepsia	Common	X			
Dysphagia	Common	X			
Intestinal obstruction	Common	X			
Nausea	Very common	X			
Stomatitis	Very common	X			
Vomiting	Very common	X			
General disorders and administration site conditions					
Asthenia	Very common	X			
Chest pain	Common	X			
Chills	Very common	X			
Fatigue	Very common	X			
Infusion site reactions	Common	X			
Lethargy	Uncommon	X			
Malaise	Uncommon	X			
Mucosal inflammation	Common	X			
Edema	Very common	X			
Pyrexia	Very common	X			

Hepatobiliary disorders					
Cholangitis	Common	X			
Hyperbilirubinemia	Common	X			
Immune system disorders					
Hypersensitivity	Uncommon	X		X	
Infections and infestations					
Lower respiratory tract infection including bronchitis	Common	X			
Candida infection	Common	X			
Folliculitis	Common				
Injection site infection	Uncommon				
Nail infection	Common				
Neutropenic sepsis	Uncommon	X		X	
Pneumonia	Common	X		X	
Sepsis	Common	X		X	
Upper respiratory tract infection	Common	X			
Urinary tract infection	Common	X			
Injury, Poisoning and Procedural Complications					
Radiation recall phenomenon [e]	Not known				
Investigations					
Alanine aminotransferase increased	Very common	X			
Aspartate aminotransferase increased	Common	X			
Blood alkaline phosphatase increased	Common	X			
Blood creatinine increased	Common	X			

Weight decreased	Very common	X			
Metabolism and nutrition disorders					
Decreased appetite	Very common	X			
Dehydration	Very common	X			
Fluid retention	Uncommon	X			
Hypokalaemia	Very common	X			
Musculoskeletal and connective tissue disorders					
Arthralgia	Very common	X			
Muscular weakness	Common	X			
Musculoskeletal pain	Very common	X			
Myalgia	Very common	X			
Nervous system disorders					
Ataxia	Common	X			
Cranial nerve palsies [e]	Not known	X			
Dizziness	Very common	X			
Dysgeusia	Very common	X			
Facial paralysis	Uncommon	X			
Headache	Very common	X			
Peripheral neuropathy [f]	Very common	X			
Vocal cord paresis [e]	Not known	X			
Psychiatric disorders					
Anxiety	Common	X			
Depression	Very common	X			
Insomnia	Very common	X			
Renal and urinary disorders					
Acute renal failure	Common	X		X	
Hematuria	Common	X			

Hemolytic uremic syndrome	Uncommon	X			
Respiratory, thoracic and mediastinal disorders					
Cough	Very common	X			
Dry throat	Uncommon				
Dyspnea	Very common	X			
Epistaxis	Very common	X			
Hemoptysis	Common	X			
Nasal congestion	Common	X			
Nasal dryness	Uncommon				
Oropharyngeal pain	Common				
Pleural effusion	Common	X			
Pneumonitis [g]	Common	X		X	
Pulmonary embolism	Common	X		X	
Radiation pneumonitis	Unknown	X			
Skin and subcutaneous tissue disorders					
Alopecia	Very common	X			
Dermatitis allergic	Uncommon	X			
Dry skin	Common	X			
Erythema	Common	X			
Erythema multiforme	Uncommon	X			
Nail disorder including onycholysis and discoloration	Very common	X			
Palmar-plantar erythrodysesthesia syndrome	Common	X			
Photosensitivity reaction[e]	Not known				
Pruritus	Very common	X			
Rash including generalized	Very common	X			

Skin exfoliation	Uncommon				
Stevens – Johnson syndrome[e]	Not known	X			
Toxic epidermal necrolysis[e]	Not known	X			
Urticaria	Uncommon	X			
Vascular disorders					
Deep vein thrombosis	Common	X			
Flushing	Common	X			
Hypertension	Common	X		X	
Hypotension	Common	X			
Lymphoedema	Common	X			

ADR = adverse drug reaction; CIOMS = Council for International Organizations of Medical Sciences; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; RSI = reference safety information; SMQ = standardized MedDRA query; WG = Working Group.

a CIOMS IV WG Criteria are defined as Very Common: ≥10%; Common: ≥1% and < 10%; Uncommon: ≥0.1% and <1%; Rare: ≥0.01% and < 0.1%; and Very Rare: < 0.01%.
b Serious ADR from any source defined as resulting in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect or considered an important medical event. c Severity corresponding to seriousness criteria of life-threatening or death. d New PTs reported since the previous RSI version. e ADRs identified in the post-marketing setting are *italicized.* In cases where the ADR was observed from both post-marketing and clinical trials, the event is classified as clinical trial.
f Peripheral neuropathy evaluated using the MedDRA SMQ neuropathy (broad scope); all PTs will be considered listed.
g Pneumonitis evaluated using the MedDRA SMQ interstitial lung disease; all PTs will be considered listed.

Note: When an ADR is reported as serious, or life-threatening or leads to death, the term will be considered unexpected for regulatory purposes, unless marked with an “X” under the corresponding column listed above.
Note: All ADRs reported in this table have been reported more than once.
Source: *nab*-Paclitaxel (Abraxane) Company Core Data Sheet (CCDS) Version 14, 29 September 2014.

9.0 DRUG INFORMATION

9.1 nab-paclitaxel (Abraxane®) - Investigational

Overview nab-Paclitaxel (ABRAXANE® for Injectable Suspension [Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, Summit, New Jersey, United States; hereafter referred to as “Celgene”], ABI-007) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel in a noncrystalline amorphous state and human albumin with a

mean particle size of approximately 130 nanometers. nab-Paclitaxel has been developed to improve the therapeutic index of paclitaxel, also reducing the toxicities associated with Taxol and the CrEL and ethanol vehicle. This may be achieved in part by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor. Because nab-paclitaxel does not contain a solvent vehicle, micellar entrapment observed with Taxol does not occur [25-27]. nabPaclitaxel displays linear pharmacokinetic (PK) characteristics. The novel albumin-bound particle formulation of paclitaxel in nab-paclitaxel conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m2 for nab-paclitaxel (Study DM97-123) versus 175 mg/m2 for Taxol [28]. The use of albumin-bound paclitaxel also enables nab-paclitaxel to be given in a shorter, more convenient infusion time of 30 - 40 minutes compared with 3 hours to 24 hours with Taxol. Due to its distinct pharmacological and PK properties and therapeutic index, nab-paclitaxel has been approved by regulatory authorities worldwide in over 40 countries/regions as a new product, rather than as a generic formulation of Taxol. nab-Paclitaxel may be given without steroid and anti-histamine premedication, which is required for Taxol to prevent solvent-related HSRs (Taxol US prescribing information). Cremophor EL has been shown to leach plasticizers, specifically di(2-ethylhexyl) phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing [29-34]. Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (e.g., carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol prescribing information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; nonPVC-containing infusion sets (e.g., those with polyethylene lining) should be used (Taxol US prescribing information). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of nab-paclitaxel [25,28].

As of October 2016, nab-paclitaxel is approved under the trade name of ABRAXANE in 65 countries worldwide for the treatment of patients with metastatic breast cancer. ABRAXANE is also approved in 54 countries worldwide for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in 57 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and in Japan for treatment of advanced gastric cancer.

Indications and Usage:
In the United States, ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin bound) is indicated for the treatment of metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

It is also indicated for the first-line treatment of locally advanced or metastatic NSCLC (non-small cell lung cancer), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy, and is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

Other names for the drug: Abraxane (ABI-007

ABRAXANE® Description
ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE® is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion.

Clinical Pharmacology

Pharmacokinetics and Drug Metabolism

Absorption
The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of ABRAXANE® at dose levels of 80 to 375 mg/m2 were determined in clinical studies. Dose levels of mg/m2 refer to mg of paclitaxel in ABRAXANE®. Following intravenous administration of ABRAXANE®, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

The drug exposure (AUCs) was dose proportional over 80 to 300 mg/m2 and the pharmacokinetics of paclitaxel for ABRAXANE® were independent of the duration of intravenous administration. The pharmacokinetic data of 260 mg/m2 ABRAXANE® administered over a 30minute infusion was compared to the pharmacokinetics of 175 mg/m2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for ABRAXANE® than for paclitaxel injection. There were no differences in terminal half-lives.

Pharmacokinetic Parameters

Distribution
Following ABRAXANE® administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with ABRAXANE® (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with ABRAXANE® compared with solvent-based paclitaxel, when the total exposure is comparable. In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel by CYP3A4. In vitro, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Elimination
At the clinical dose range of 80 to 300 mg/m2, the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m2, and the mean terminal half-life ranges from 13 to 27 hours. After a 30-minute infusion of 260 mg/m2 doses of ABRAXANE®, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-p-hydropaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

Specific Populations

Pharmacokinetics in Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of paclitaxel following ABRAXANE® administration was studied in patients with advanced solid tumors. The results showed that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN, AST ≤10 x ULN, n=8) had no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin >1.5 to ≤3 x ULN, AST ≤10 x ULN, n=7) or severe (total bilirubin >3 to ≤5 x ULN, n=5) hepatic impairment had a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function (total bilirubin ≤ ULN, AST ≤ ULN, n=130)

Elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamics modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for ABRAXANE® exposure. Pharmacokinetic data are not available for patients with total bilirubin >5 x ULN or for patients with metastatic adenocarcinoma of the pancreas.

Pharmacokinetics in Renal Impairment
The effect of pre-existing mild (creatinine clearance ≥60 to <90 mL/min, n=61) or moderate (creatinine clearance ≥30 to <60 mL/min, n=23) renal impairment on the pharmacokinetics of paclitaxel following ABRAXANE® administration was studied in patients with advanced solid tumors. Mild to moderate renal impairment had no clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

Other Intrinsic Factors
Population pharmacokinetic analyses for ABRAXANE® show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m2), gender, race (Asian vs. White), age (24 to 85 years) and type of solid tumors do not have a clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

Pharmacokinetic Interactions between ABRAXANE® and Carboplatin
Administration of carboplatin immediately after the completion of the ABRAXANE® infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The observed mean AUCinf of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

Description
Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

Classification - type of agent: Antineoplastic Agent

Mode of action:
Paclitaxel protein-bound, an albumin-bound form of paclitaxel (a natural product obtained from Taxus media), works as an anti-microtubule agent by promoting microtubule assembly from tubulin dimers and stabilizing microtubules. Stabilizing microtubules prevents depolymerization and causes an inhibition of the normal dynamic reorganization of the microtubules which is necessary for important interphase and mitotic functions in the cell. Paclitaxel causes the formation of abnormal bundles of microtubules in many phases of the cell cycle and multiple asters of microtubules during mitosis

Pharmacokinetics: *nab*-Paclitaxel displays linear pharmacokinetic (PK) characteristics. Hepatic metabolism and biliary excretion are likely routes of paclitaxel elimination in humans.

Patients with mild hepatic impairment (total bilirubin > 1 to ≤1.5 x Upper limit of normal [ULN]) have no clinically important changes in pharmacokinetics (PK) of paclitaxel while patients with moderate (total bilirubin >1.5 to ≤3 x ULN) or severe (total bilirubin >3 to ≤5 x ULN) hepatic impairment have a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function. Mild to moderate renal impairment (creatinine clearance ≥30 and < 90 mL/min) has no clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

Elimination half-life, 13 to 27 hours

Side effects:
Common

a) Cardiovascular: Edema (10%), Electrocardiogram abnormal (60%), Peripheral edema (non-small cell lung cancer, 10%; pancreatic cancer, 46%)Dermatologic: Alopecia (breast cancer, 90%; non-small cell lung cancer, 56%; pancreatic cancer, 50%), Rash (non-small cell lung cancer, 10%; pancreatic cancer, 30%)

b) Gastrointestinal: Constipation (non-small cell lung cancer, 16%), Diarrhea (breast cancer, 27%; non-small cell lung cancer, 15%; pancreatic cancer, 44%), Loss of appetite (nonsmall cell lung cancer, 17%; pancreatic cancer, 36%), Nausea, Any grade (breast cancer, 30%; non-small cell lung cancer, 27%; pancreatic cancer, 54%), Vomiting, Any grade (breast cancer, 18%; non-small cell lung cancer, 12%; pancreatic cancer, 36%)

c) Hematologic: Anemia (breast cancer, 33%; non-small cell lung cancer, 98%), Neutropenia, Any grade (73% to 85%), Thrombocytopenia (breast cancer, 2%; non-small cell lung cancer, 68%; pancreatic cancer, 74%)

d) Hepatic: Alkaline phosphatase raised (36%), AST/SGOT level raised (39%), Gamma-

glutamyl transferase raised, Grade 3 or 4 (14%)

e) Musculoskeletal: Arthralgia (11% to 13%), Myalgia (10%)

f) Neurologic: Asthenia (breast cancer, 47%; non-small cell lung cancer, 16%; pancreatic cancer, 19%), Peripheral neuropathy (non-small cell lung cancer, 48%; pancreatic cancer, 54%), Sensory neuropathy, Any grade (71%)

g) Ophthalmic: Visual disturbance (13%)

h) Renal: Serum creatinine raised (11%)

i) Respiratory: Dyspnea (12%)

j) Other: Dehydration (pancreatic cancer, 21%), Fatigue (non-small cell lung cancer, 25%; pancreatic cancer, 59%), Fever (pancreatic cancer, 41%)

Serious

a) Cardiovascular: Cardiac arrest, Cerebrovascular accident, Supraventricular tachycardia, Transient ischemic attack

b) Gastrointestinal: Nausea, Grade 3 or higher (breast cancer, 3%; pancreatic cancer, 6%), Vomiting, Grade 3 or higher (4% to 6%)

c) Hematologic: Anemia, Severe (breast cancer, 1%; non-small cell lung cancer, 28%), Febrile neutropenia (2%), Hemorrhage (2%), Neutropenia, Grade 3 or 4 (breast cancer, 9%; non-small cell lung cancer, 47%; pancreatic cancer, 38%), Thrombocytopenia, Severe (breast cancer, less than 1%; non-small cell lung cancer, 18%; pancreatic cancer, 13%), Thrombosis

d) Immunologic: Anaphylaxis, Hypersensitivity reaction (4%), Infectious disease (24%)

e) Neurologic: Cranial nerve disorder, Sensory neuropathy, Grade 3 (10%), Vocal cord palsy

f) Respiratory: Pneumonia (3% to 4%), Pneumonitis (pancreatic cancer, 4%), Pneumothorax (less than 1%), Pulmonary embolism, Pulmonary thromboembolism

g) Other: Neutropenic sepsis (less than 5%), Sepsis (pancreatic cancer, 5%)

Drug Interactions

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Pharmacokinetic drug-drug interactions between *nab*-paclitaxel and inhibitors or inducers of CYP2C8 or CYP3A4 have not been evaluated in humans.

Storage and stability

Unopened vials of *nab*-paclitaxel are stable until the date indicated on the package when stored in the original cartons at United States Pharmacopeia (USP) Controlled Room Temperature (20°C to 25°C, excursions permitted between 15° to 30°C), or as specified on the vial label and as per the country requirements.

Preparation and Dispensing

nab-Paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use. Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. Using a sterile syringe, slowly inject 20 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to a vial of *nab*-paclitaxel. Direct the solution flow onto the inside wall of the vial and take at least 1 minute for the introduction. Do not inject the solution directly onto the lyophilisate as this will result in foaming. Once the addition is complete, allow the vial to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any lyophilisate occurs. Avoid the generation of foam.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient and slowly withdraw the dosing volume of the reconstituted *nab*-paclitaxel suspension from the vial(s) into a syringe. The exact total dosing volume of 5 mg/mL suspension required for the patient is calculated using the following formula:

Dosing volume (mL) = Total dose (mg) / 5 (mg/mL)

Administration

Inject the appropriate amount of reconstituted *nab*-paclitaxel into an empty, sterile, intravenous bag (PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer *nab*-paclitaxel infusions. The use of medical devices containing silicone oil as a lubricant (i.e., syringes and IV bags) to reconstitute and administer *nab*-paclitaxel may result in the formation of proteinaceous strands. Visually inspect the reconstituted *nab*-paclitaxel suspension in the IV bag prior to administration. If strands are observed, administer reconstituted *nab*-paclitaxel suspension through a 15 micron filter. Do not use a filter with a pore size less than 15 microns. A similar phenomenon has also been

observed with other protein-containing injectable products. Filtration of the *nab*-paclitaxel suspension using a 15 micron filter removes the proteinaceous strands and does not change the physical or chemical properties of *nab*-paclitaxel suspension. Based on data from clinical trials and post-marketing surveillance, there is no indication of an increased risk of embolic events should these strands be administered to patients. Refer to local product label or study notebook, as applicable, for complete directions regarding the use of a filter.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever the solution and container permit. The reconstituted sample should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use.

Following administration of *nab*-paclitaxel, the intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

Dose Reduction / Discontinuation Recommendations
Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. Please refer to the Prescribing Information which can be found in Section 2.5.

Availability
Provided by Celgene Corporation
Under no circumstance will the study medication *nab*-paclitaxel be used other than as directed by the protocol. Do Not Use Commercially Available Product.

Supplier(s)
ABRAXANE® will be supplied by Celgene Corporation and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number AX-BLD-12813, product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements and/or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, site must order Abraxane, depending on the study IND status. For IND studies, site should be order Abraxane through the Endpoint (IDOS) online drug ordering system. For IND Exempt studies, site must submit a completed Celgene USMA IND Exempt Drug Request Form, the most recent IRB approval letter, and the most current drug accountability log for your study to the following mailbox: NonIMIDUSOrders@celgene.com (Fax number: 844-343-4312). Allow 5 working days for drug shipment and note there are no drug shipments on Fridays and holidays.

Drug Accountability:
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug *nab*-paclitaxel. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

Receipt of study drug
The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug nab-paclitaxel. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

Return and Retention of Study Drug

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty vials or unused vials to the clinic site.

Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue, Building L
Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

9.2 Pembrolizumab (Keytruda®) – Standard of Care

Other names for the drug: Keytruda®

Please refer to the package insert for pembrolizumab for details of storage, administration etc.

Availability/ordering

Commercially available. Standard of care.

10.0 CORRELATIVES/SPECIAL STUDIES

We will archive patient tumor, plasma and serum samples for future unspecified testing including but not limited to PD-L1 and anti-drug antibody testing. Submission of samples for correlative studies is expected of all subjects at baseline and optional tumor biopsy will be performed for those who consent to it.

10.1 Sample Collection Guidelines

Tumor Tissue

An archived tissue block must be identified to submit unstained slides prior to registration. Unstained slides from an archived formalin-fixed paraffin embedded tissue block are to be submitted for each subject from prior cystectomy or biopsy of metastatic lesion (estimated tumor content >30% of nucleated cells in specimen) to create a tissue archive of these patients.

Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, must be identified to submit for determination of sufficient viable tumor content prior to study enrollment. Tumor specimens will be evaluated for PD-L1 expression at a future time when funding is secured.

Blood Collection for Banking

Whole blood samples (20 mL)

Serum samples (5-10 mL)
Serum processing: Collect whole blood in a covered test tube. If commercially available tubes are to be used, the researcher should use the red topped tubes. These are available from Becton Dickinson (BD). BD's trade name for the blood handling tubes is Vacutainer. After collection of the whole blood, allow the blood to clot by leaving it undisturbed at room temperature. This usually takes 15-30 minutes. Remove the clot by centrifuging at 1,000-2,000 x g for 10 minutes in a refrigerated centrifuge.

The resulting supernatant is designated serum. Following centrifugation, it is important to immediately transfer the liquid component (serum) into a clean polypropylene tube using a Pasteur pipette. The samples should be maintained at 2-8°C while handling. The serum should be apportioned into 0.5 ml aliquots, stored, and transported at –20°C or lower. It is important to avoid freeze-thaw cycles because this is detrimental to many serum components. Samples which are hemolyzed, icteric or lipemic can invalidate tests.

Plasma samples (5-10 mL)
Plasma Collect whole blood into commercially available anticoagulant-treated tubes e.g., EDTA-treated (lavender tops) or citrate-treated (light blue tops). Heparinized tubes (green tops) are not permitted. Cells are removed from plasma by centrifugation for 10 minutes at 1,000-2,000 x g using a refrigerated centrifuge. Centrifugation for 15 minutes at 2,000 x g depletes platelets in the plasma sample.

The resulting supernatant is designated plasma. Following centrifugation, it is important to immediately transfer the liquid component (plasma) into a clean polypropylene tube using a Pasteur pipette. The samples should be maintained at 2-8°C while handling. If the plasma is not analyzed immediately, the plasma should be apportioned into 0.5 ml aliquots, stored, and transported at –20°C or lower. It is important to avoid freeze-thaw cycles.

10.2 Specimen Banking

Patient samples (plasma and serum) collected for this study will be retained at the University of Michigan. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories

11.0 STATISTICAL CONSIDERATIONS

The primary aim of this single-arm phase 2 trial is to determine the efficacy of the combination of pembrolizumab and abraxane in patients with advanced urothelial carcinoma. The primary endpoint is the ORR (Overall Response Rate = Complete Response + Partial Response per RECIST 1.1) proportion.

11.1 Study Design

Historical ORR in these subjects (both platinum-refractory and cisplatin- ineligible) treated with anti-PD1/PDL1 is 16-23%. For study design purposes, we state that an ORR of <25% with the combination of pembrolizumab and abraxane would be uninteresting and an ORR of 45% or greater would be interesting for further investigation. We will utilize a **Simon's two-stage minimax design with 17 response evaluable patients in stage 1 and 19 additional response evaluable patients possible in stage 2** for a **total sample size of 36 response evaluable**

patients. This design will provide 80% power with a 5% type I error. If 4 or less responses are found in stage 1, then the combination will be considered uninteresting for further study. If 5 or more responses are in stage 1, then stage 2 will be opened to accrual. After accrual of 36 response evaluable patients, if 14 or more responses are observed then the combination treatment will be declared interesting for further study. This trial design has a 57% probability of terminating early if the true response rate is < 25% and only 6% probability of early termination if the true response rate is 45% or greater. Response evaluable is defined below.

Interim Analysis in the Simon's two-stage mini-max design:
After 17 response evaluable patients have been accrued in stage 1, an interim efficacy analysis will be done. If 4 or fewer responses are observed, then the trial will stop and the combination will be deemed uninteresting for further investigation. If 5 or more responses are observed, then stage 2 will be opened and 19 more response evaluable patients will be accrued.

Populations for Analysis
Intent-to-Treat Population: All patients consented and enrolled in the trial.

Response Evaluable Population: Only those patients who have had their disease re-evaluated by imaging after 2 cycles of therapy OR exhibit objective or unequivocal clinical disease progression prior to the end of cycle 2 will be considered evaluable for the primary endpoint.

Safety Evaluable Population: Patients who receive any treatment on protocol will be considered evaluable for safety.

11.2 Sample Size and Accrual

The planned accrual for Stage 1 of the Simon two-stage trial is 17 subjects. If the criterion for the interim efficacy analysis (as above) is met, the study will move on to Stage 2 for an additional accrual of 19 subjects more.

Accrual for Stage 1 is expected to be over 12 months at the University of Michigan.

Accrual for Stage 2 (if applicable) will be over an additional 12 months at the University of Michigan.

11.3 Data Analyses Plans

Primary Analysis:
The primary efficacy endpoint is best overall response rate. The primary analysis will include the response count and proportion with the associated exact 95% binomial confidence interval in the response evaluable population. If stage 2 is initiated, then the efficacy analysis methods for the reported response confidence interval will be as described by Koyama and Chen [32]. A secondary analysis in the intent-to-treat population will be reported. Patients who are unable to receive 2 cycles of treatment due to toxicity will be considered non-responders in the intent-to-treat analysis.

Secondary Endpoint Analysis:
Safety and Toxicity of pembrolizumab and abraxane will be listed and tabulated by organ system per CTCAE grade version 4.03. The number of cycles, dose reductions and dose delays will be described. All safety and toxicity analyses will be done on the Safety evaluable population.

Time-to-event endpoints including PFS (Progression-Free Survival), DOR (Duration of Response) and OS (Overall Survival) will be described using Kaplan-Meier methods. Kaplan-Meier plots and median, 12-month and 24-month product limit estimates with 95% confidence intervals will be reported. DOT (Duration of Therapy) will be described

using a median and inter-quartile range. CR (Complete Response) proportion will be reported with a count, proportion and associated 95% exact binomial confidence interval.

Correlative analysis:
PD-L1 expression in tumor tissue and TILs at baseline (and in optional tumor biopsy at progression) will be reported when such testing is performed with count and proportions and 95% confidence intervals, and correlated with response using chi-square tests and logistic models.

Exploratory analysis:
Development of a Therapy Response Predictor based on baseline (and separately in optional tumor biopsy tissue at progression when available) immune parameters in tissue will be explored using logistic models. Elastic net and random forest methods will be used and compared to develop the predictor model. Quality of Life with patient-reported outcomes (EQ-5D-5L) will be described using means or medians and associated measures of variability.

12.0 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports

If the FDA has granted an IND, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to

Celgene Corporation as a supporter of this study as follows:

Celgene Corporation
Attn: Medical Affairs Operations
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

13.0 DATA MANAGEMENT

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web based electronic data capture (EDC) system of the University of Michigan.

CRFs will be reviewed and source verified during annual monitoring visits. Discrepant, unusual and incomplete data will be queried by the Quality Assurance Monitoring Team. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

14.0 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan.

The study team will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee (DSMC) on a quarterly basis for independent review.

15.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g., FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, investigator must immediately inform the CTO that such a request has been made.

16.0 REFERENCES

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17.0 APPENDICES

APPENDIX 1

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 2

EQ-5D-5L

Health Questionnaire

English version for the USA

Check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ⑨

I have slight problems walking ⑨

I have moderate problems walking ⑨

I have severe problems walking ⑨

I am unable to walk ⑨

SELF-CARE

I have no problems washing or dressing myself ⑨

I have slight problems washing or dressing myself ⑨

I have moderate problems washing or dressing myself ⑨

I have severe problems washing or dressing myself ⑨

I am unable to wash or dress myself ⑨

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ⑨

I have slight problems doing my usual activities ⑨

I have moderate problems doing my usual activities	⑨
I have severe problems doing my usual activities	⑨
I am unable to do my usual activities	⑨

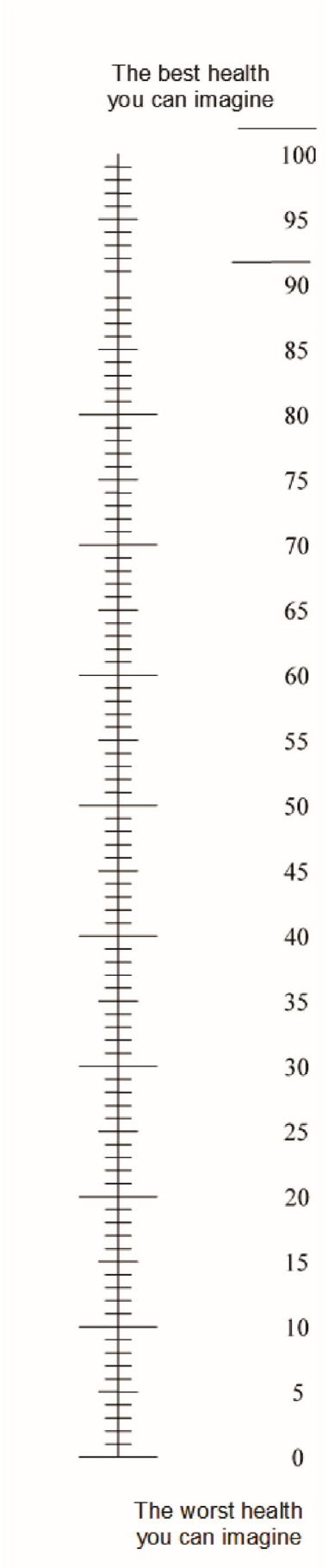
PAIN / DISCOMFORT

I have no pain or discomfort	⑨
I have slight pain or discomfort	⑨
I have moderate pain or discomfort	⑨
I have severe pain or discomfort	⑨
I have extreme pain or discomfort	⑨

ANXIETY / DEPRESSION

I am not anxious or depressed	⑨
I am slightly anxious or depressed	⑨
I am moderately anxious or depressed	⑨
I am severely anxious or depressed	⑨
I am extremely anxious or depressed	⑨

We would like to know how good or bad your health is TODAY.



This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐