A Phase Ib/II Study of Anti-PD-1 Antibody Pembrolizumab and Imprime PGG for Patients with Metastatic Non-small Cell Lung Cancer After Progression on First-Line Therapy: Big Ten Cancer Research Consortium BTCRC-LUN15-017

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## PROTOCOL SIGNATURE PAGE

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**VERSION DATE: 29OCT2020**

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

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to BTCRC Administrative Headquarters and keep a record for your files.

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

**PLEASE COMPLETE AND EMAIL TO BTCRC ADMINISTRATIVE HEADQUARTERS**

# STUDY SYNOPSIS

| | |
|---|---|
| **TITLE** | A Phase Ib/II Study of Anti-PD-1 Antibody Pembrolizumab and Imprime PGG for Patients with Metastatic Non-small Cell Lung Cancer After Progression on First-Line Therapy |
| **PHASE** | Phase Ib/II |
| **OBJECTIVES** | **Primary Objectives:**<br>**Phase Ib Dose Escalation Cohort**: To establish the maximum tolerated dose (MTD) of Imprime PGG in combination with pembrolizumab for subjects with metastatic non-small cell lung cancer (NSCLC) after progression on first-line platinum-based chemotherapy.<br>**Phase II Study:** To estimate progression-free survival (PFS) using RECIST v1.1 in subjects with metastatic NSCLC treated with Imprime PGG in combination with pembrolizumab after progression on first-line systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy) based on RECIST v1.1.<br>**Secondary Objectives for Phase Ib:**<br>• Characterize adverse effects (AEs) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line platinum-based chemotherapy.<br>• Estimate clinical benefit rate (CBR: complete response, partial response, or stable disease) measured by RECIST v1.1 of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line platinum-based chemotherapy.<br>• Estimate Progression-Free Survival (PFS) and 6 month PFS using RECIST v1.1 in subjects with NSCLC who progressed after first-line platinum-based chemotherapy when treated with Imprime PGG in combination with pembrolizumab.<br>• Estimate overall survival (OS) and 1-year OS in subjects with NSCLC who progressed after first-line platinum-based chemotherapy when treated with Imprime PGG in combination with pembrolizumab.<br>**Secondary Objectives for Phase II:**<br>• Characterize adverse effects (AEs) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line systemic therapy.<br>• Estimate clinical benefit rate (CBR: complete response, partial response, or stable disease) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line systemic therapy.<br>• Estimate Progression-Free Survival (PFS) and 6 month PFS using RECIST v1.1 in subjects with NSCLC when treated with Imprime PGG in combination with pembrolizumab who progressed after first-line systemic therapy.<br>• Estimate overall survival (OS) and 1-year OS in subjects with NSCLC when treated with Imprime PGG in combination with pembrolizumab who progressed after first-line systemic therapy.<br>**Correlative Objectives for Phase Ib/II Study:**<br>• Correlate biomarkers on immune cell subsets (including, but not limited to monocytes, macrophages, granulocytes, and lymphocytes, and PD-L1) concentrations and localization (peri- vs. intratumoral) in archived diagnostic tumor tissue with PFS and CBR.<br>• Correlate change in soluble PD-L1 levels pre-dose Cycles 2 and 3, relative to |

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| | baseline (i.e., pre-dose Day 1 of Cycle 1) level with PFS and CBR.<br>• Correlate PD-L1 expression on circulating peripheral mononuclear cells from whole blood pre-dose Cycles 2 and 3, relative to baseline (i.e., pre-dose Day 1 of Cycle 1) level.<br>• Correlate anti-β-glucan antibody (ABA) (IgM, IgG) levels with PFS and CBR.<br>• Correlate proteomic immune classifiers at baseline with PFS and CBR.<br>• Correlate FcγRIIa polymorphism to PFS and CBR. |
| **STUDY DESIGN** | Single arm study with dose escalation Phase Ib cohort followed by a Phase II cohort |
| **KEY INCLUSION CRITERIA** | 1. Subjects with histologically or cytologically confirmed non-small cell lung cancer (NSCLC).<br>2. Subjects with stage IV non-small cell lung cancer (NSCLC) as defined by American Joint Committee on Cancer (AJCC) 7th Edition. Patients with locally advanced or recurrent disease who are candidates for systemic therapy are also allowed.<br>3. Subjects without EGFR activating mutation (Exon 19 del, L858R) or ALK, ROS translocation if histology is adenocarcinoma. Subjects with an EGFR activating mutation or ALK translocation are eligible only after failing TKI therapy (such as gefitinib, erlotinib, or afatinib). Furthermore, if a T790M resistance mutation is found, the patient must have failed a 3rd generation TKI such as osimertinib.<br>4. Phase Ib: Subjects who progressed after first-line platinum-based chemotherapy and who are candidates for second-line therapy.<br>Phase II: Subjects who progressed after first-line systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy) who are candidates for second-line systemic therapy. Patients with early stage cancer will also be eligible if progression occurs:<br>a. within 6 months of adjuvant chemotherapy after curative resection<br>b. within 6 months of adjuvant chemotherapy after curative resection while on adjuvant immunotherapy, currently only available as part of a clinical trial<br>c. within 6 months of curative surgery if chemotherapy is given in the neoadjuvant setting<br>d. within 6 months of completion of chemoradiation (or 6 months from completion of consolidation chemotherapy if administered after concurrent chemoradiation)<br>e. within 6 months of completion of chemoradiation or consolidation chemotherapy (if administered) while on consolidation immunotherapy, a setting for which durvalumab is FDA approved.<br>Phase II: Subjects with an EGFR or ALK mutation who are no longer candidates for TKI therapy and have progressed on standard systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy).<br>5. Phase II only: Measurable disease according to RECIST v1.1 (Section 8) obtained by imaging within 28 days prior to study registration.<br>Phase Ib: subjects may enroll with or without measurable disease.<br>6. Has an Eastern Cooperative Oncology Group (ECOG) performance status of |

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| | 0, 1, or 2 within 28 days prior to study registration.<br>7. Adequate hepatic function within 28 days prior to study registration defined as meeting **all** of the following criteria:<br>a. total bilirubin ≤ 1.5 × upper limit of normal (ULN) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN (except subject with Gilbert's Syndrome, who must have total bilirubin < 3.0 mg/dl)<br>b. aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases<br>c. alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases<br>8. Adequate renal function within 28 days prior to study registration defined by **either** of the following criteria:<br>a. serum creatinine ≤ 3 × ULN<br>b. if serum creatinine > 3 × ULN, estimated glomerular filtration rate (GFR) ≥ 20 mL/min<br>9. Adequate hematologic function within 28 days prior to study registration defined as meeting **all** of the following criteria:<br>a. hemoglobin ≥ 9 g/dL; subjects requiring transfusion <u>will</u> be eligible to start study.<br>b. absolute neutrophil count (ANC) ≥ $1.5 \times 10^9$/L<br>c. platelet count ≥ $100 \times 10^9$/L<br>10. Adequate coagulation functioning within 28 days prior to study registration defined by **either** of the following criteria:<br>a. INR < 1.5 × ULN<br>b. for subjects receiving anticoagulation, the subjects must, in the investigator's opinion, be clinically stable with no evidence of active bleeding while receiving anticoagulant therapy. The INR for these subjects should be in therapeutic range. Low molecular weight heparin (LMWH) is allowed. |
| **TREATMENT PLAN** | <u>Phase Ib</u>: Dosing will occur in 21-day cycles. Imprime PGG in this dose escalation study will be dosed at 2 mg/kg IV or 4 mg/kg IV on Day 1, 8, and 15 of each 21 day cycle. On Day 1 of each cycle, pembrolizumab will be infused at 200 mg. On Day 1 of each cycle, the Imprime PGG intravenous infusion is given first followed 15-30 minutes later by the pembrolizumab infusion. Imprime PGG will be administered as a 2-4 hour intravenous infusion (based on dose and on the subject's weight). Pembrolizumab will be administered as a 30-minute intravenous infusion. Subsequent cycles beyond Cycle 1 must meet the criteria found in section 6.1.<br><u>Phase II</u>: Imprime PGG will be dosed at the dose established in Phase 1b (4 mg/kg) on Day 1, 8, and 15 of each 21 day cycle for the first 4 cycles (12 weeks) and on Day 1 for Cycles 5-16. On Day 1 of each cycle, pembrolizumab will be infused at 200 mg. On Day 1 of each cycle, the Imprime PGG intravenous infusion is given first followed 15-30 minutes later by the pembrolizumab infusion. Imprime PGG will be administered as a 2-4 hour intravenous infusion (based on dose and on the subject's weight). Pembrolizumab will be administered as a 30-minute intravenous infusion. Subsequent cycles beyond Cycle 1 must meet the criteria found in section 6.1. |

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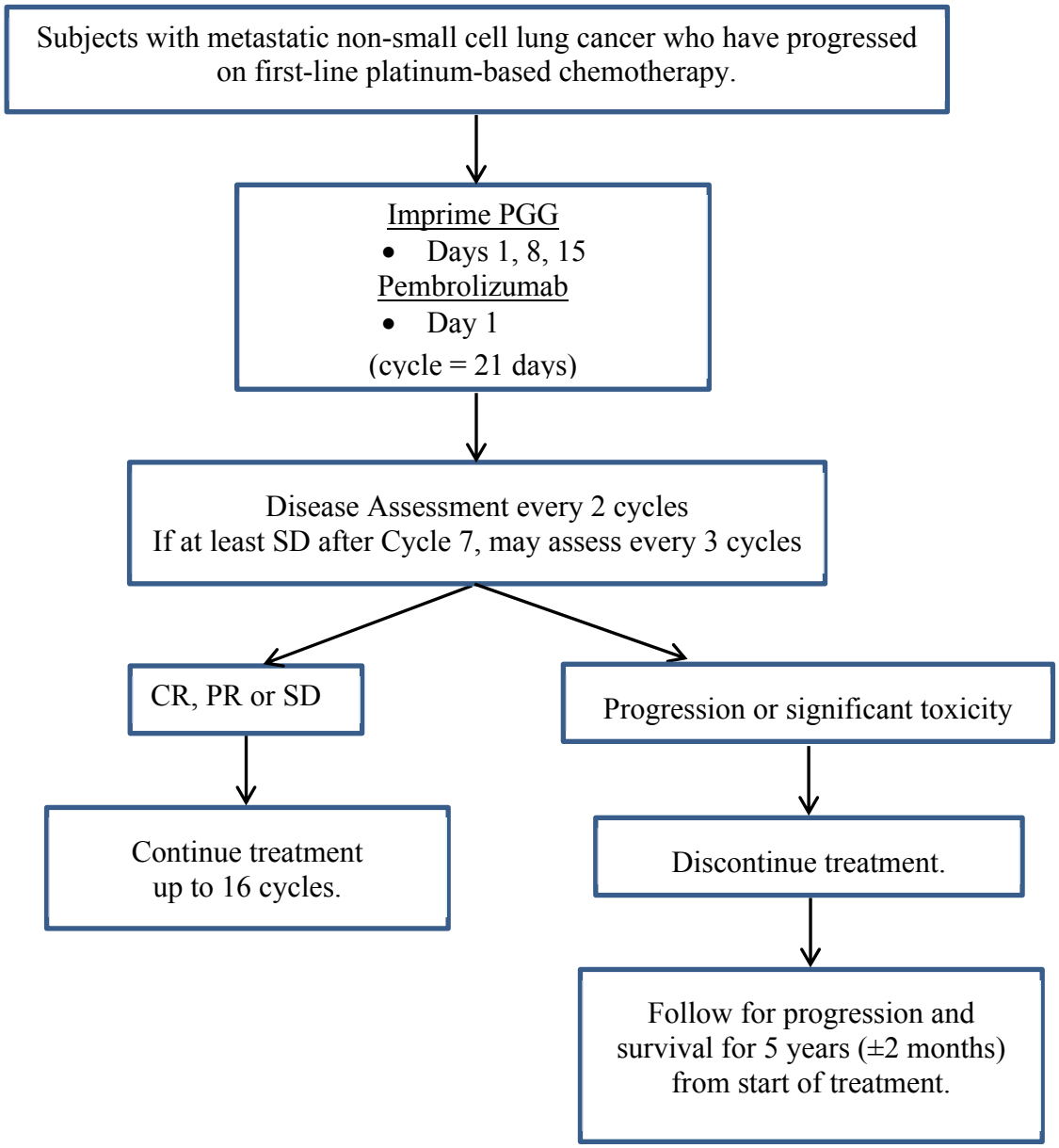
| **STATISTICAL CONSIDERATIONS** | **Phase Ib:** A standard "3+3" design will be used with maximum number of subjects accrued to be 12.<br>**Phase II:** For this single arm Phase II study, study endpoint will be median PFS as assessed by the RECIST v1.1 criteria.<br>The null hypothesis is that median PFS of combination drug is 3.2 months (equal to single agent pembrolizumab among subjects with a proportion score of 1 to 49%); the alternative hypothesis is that the PFS is 6.3 months (equal to single agent pembrolizumab among subjects with a proportion score of ≥ 50%).<br>With a total sample size of 24 the study will have 90% power to detect a difference of 3.1 months (i.e., 6.3 months versus 3.2 months), controlling for a two-sided type I error probability of 5%. The power analysis was conducted using the power calculation for one arm survival design proposed by Lawless[39].<br>Unevaluable subjects will be replaced. |
| **TOTAL NUMBER OF SUBJECTS** | Up to 36 (up to 12 in dose escalation phase and up to 24 in Phase II study) |
| **ESTIMATED ENROLLMENT PERIOD** | 18 months |
| **ESTIMATED STUDY DURATION** | 30 months |

# INDEX

## PHASE Ib SCHEMA

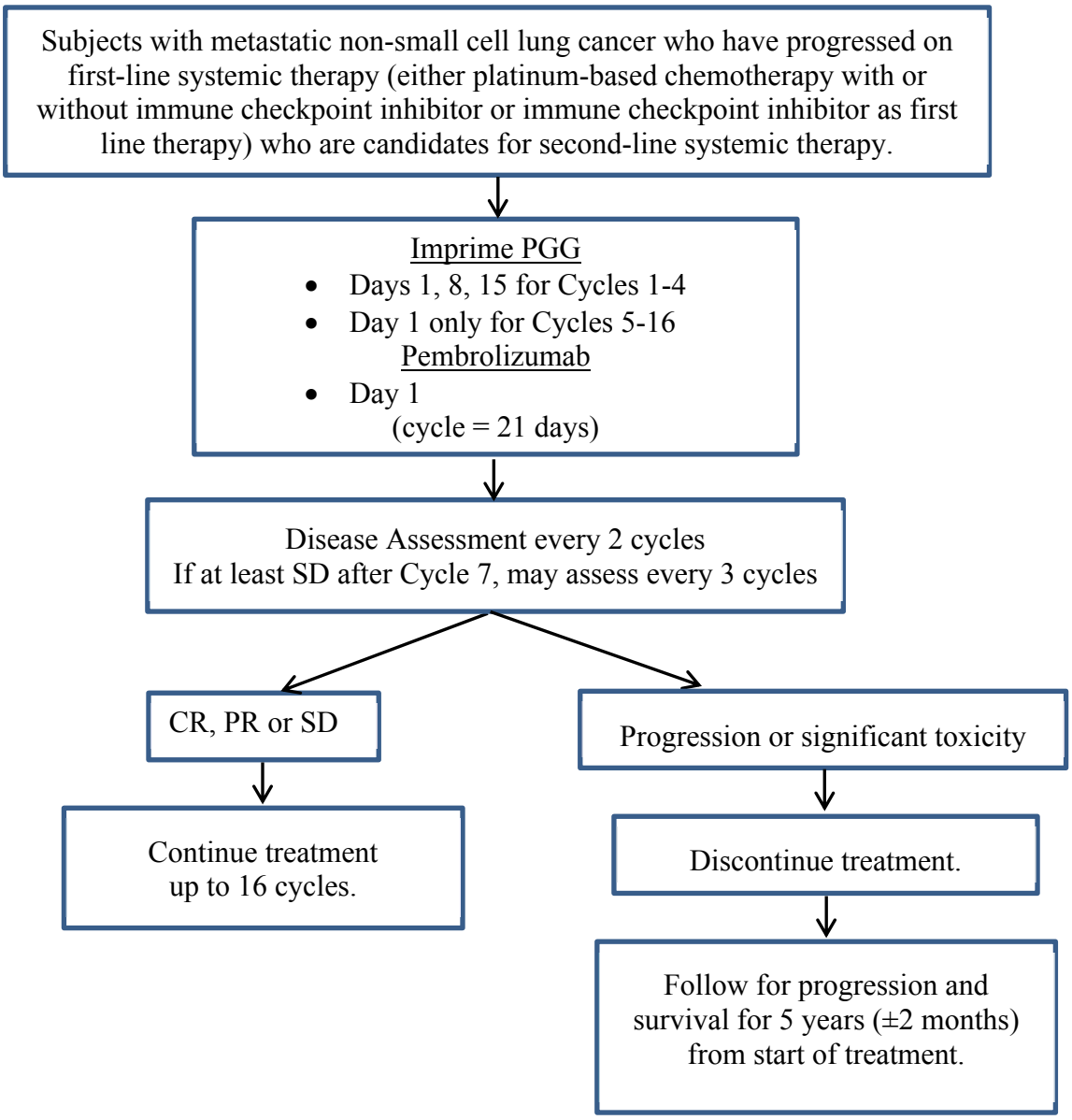
The primary objective of the phase Ib study is to establish the maximum tolerated dose of Imprime PGG in combination with Pembrolizumab for subjects with metastatic non-small cell lung cancer after progression on first-line platinum-based chemotherapy.




| Dose Cohort | # of Subjects | Imprime PGG (mg/kg) | Pembrolizumab (mg) |
|---|---|---|---|
| 1 | 3-6 | 2 | 200 |
| 2 | 3-6 | 4 | 200 |

## PHASE II SCHEMA

The primary objective of the Phase II Study is to estimate Progression-Free Survival (PFS) using RECIST v1.1 in subjects with metastatic non-small cell lung cancer treated with Imprime PGG in combination with pembrolizumab after progression on first-line systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy).




Subjects will be treated with pembrolizumab at a 200 mg dose and the recommended phase II dose of Imprime PGG.

# ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ABA | Anti-beta-glucan antibody |
| AE | adverse event |
| AHQ | Administrative Headquarters |
| ANC | absolute neutrophil count |
| Anti-PD-1 antibody | anti-programmed death 1 antibody |
| Anti-PD-L1 antibody | anti-programmed death-ligand 1 antibody |
| ALK | Anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| ASCO | American society of clinical oncology |
| AST | aspartate aminotransferase |
| ATE | arterial thromboembolic event |
| BCG | Bacillus Calmette–Guérin |
| BMP | basic metabolic panel |
| BOR | best overall response |
| BTCRC | Big Ten Cancer Research Consortium |
| C1D1 | Cycle 1 day 1 |
| CA | cancer antigen |
| CBC | complete blood cell count |
| CBR | clinical benefit rate |
| CI | Confidence interval |
| CIK | cytokine-induced killer |
| CLM | Correlative Laboratory Manual |
| cm | Centimeter |
| CNS | Central nervous system |
| CR | complete response |
| CR3 | Complement receptor 3 |
| CR3-DCC | Complement Receptor3-dependent cell mediated cytotoxicity |
| CT | computed tomography |
| CTC | cytotoxic T cell |
| CTCAE | (NCI) Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| CTLA4 | cytotoxic T-lymphocyte-associated antigen 4 |

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|---|---|
| dL | Deciliter |
| DLT | dose-limiting toxicity |
| DSMC | Data Safety Monitoring Committee |
| ECI | event of clinical interest |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| ECOG | Eastern Cooperative Oncology Group |
| eGFR | Estimated Glomerular Filtration Rate |
| EGFR | epidermal growth factor receptor |
| FDA | Food and Drug Administration |
| FDG PET/CT | fluorine 18 fluorodeoxyglucose positron emission tomography/ computed tomography |
| HBsAg | Hepatitis B surface antigen |
| HCl | Hydrochloric acid |
| Hgb | Hemoglobin |
| HepC | Hepatitis C |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| hr | Hour |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| I/O | input/output |
| IRB | Institutional Review Board |
| irAEs | Immune related adverse events |
| irBOR | Immune related best overall response |
| irCR | Immune related complete response |
| irECI | Immune related event of clinical interest |
| irPD | Immune related progressive disease |
| irPR | Immune related partial response |
| irPD | Immune related progressive disease |

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|---|---|
| IUD | Intra uterine device |
| IV | Intravenous |
| IVRS | Interactive voice response system |
| kg | Kilogram |
| LAK | lymphocyte-activated killer |
| lb | Pound |
| LDH | lactate dehydrogenase |
| LMWH | low-molecular-weight heparin |
| mCRC | metastatic colorectal cancer |
| MDSC | myeloid-derived suppressor cell |
| mg | Milligram |
| min | Minute |
| mL | Milliliter |
| $mm^3$ | cubic millimeters |
| MRI | Magnetic resonance imaging |
| MTD | maximum tolerated dose |
| MTV | metabolic tumor volume |
| N/A | Not applicable |
| NaOH | Sodium hydroxide |
| NCI | National Cancer Institute |
| NDC | National Drug Code |
| NK Cells | Natural Killer Cells |
| NS | Normal saline |
| NSAID | Non steroidal anti-inflammatory drugs |
| NSCLC | Non-small cell lung cancer |
| OS | overall survival |
| PD | Progressive disease |
| PD-1 | programmed death 1 |
| PD-L1 | programmed death ligand 1 |
| PD-L2 | programmed death ligand 2 |
| PET-CT | positron emission tomography/ computed tomography |
| PFS | progression-free survival |
| PT | Prothrombin time |
| PK | Pharmacokinetics |
| PR | partial response |
| RECIST | Response Evaluation Criteria in Solid Tumors |

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| RP2D | Recommend phase 2 dose |
| RPLS | Reversible Posterior Leukoencephalopathy Syndrome |
| RR | response rate |
| SAE | serious adverse event |
| SPD | sum of the products of the two largest perpendicular diameters |
| SD | stable disease |
| T3 | Triiodothyronine |
| T4 | Free thyroxine |
| TAA | tumor-associated antigen |
| TAM | tumor-associated macrophage |
| TNF | Tumor Necrosis Factor |
| TIL | tumor-infiltrating lymphocyte |
| TKI | tyrosine kinase inhibitor |
| TSA | tyramide signal amplification |
| TSH | Thyroid stimulating hormone |
| UI-Health | University of Illinois Health |
| ULN | upper limit of normal |
| UPIRSO | unanticipated problems involving risk to subjects or others |
| US | United States |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |
| WOCP | women of childbearing potential |
| wt | Weight |

# 1. BACKGROUND AND RATIONALE

## 1.1. Introduction

Lung cancer is one of the most commonly diagnosed cancers worldwide with 1.8 million cases that account for 13.0% of the total. It is also one of the leading causes of death worldwide accounting for 1.6 million or 19.4% of all cancer related deaths.[1] Historically, one management algorithm was applied to all patients with non-small cell lung cancer (NSCLC). A platinum agent combined with pemetrexed (for nonsquamous), paclitaxel, docetaxel, vinorelbine, or gemcitabine was recommended for first-line chemotherapy.

More recently (May 10, 2017) the U.S. Food and Drug Administration (FDA) approved the immune checkpoint inhibitor (as described below) pembrolizumab in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC).[2] Just prior to that time (October 24, 2016) the FDA approved pembrolizumab as monotherapy for second-line therapy in patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] greater than or equal to 50%) as determined by an FDA-approved test.[3]

Second-line chemotherapy at the time of disease progression could include docetaxel, or pemetrexed and erlotinib was recommended as second/third-line therapy.[4] Commonly used 2nd line therapy for NSCLC creates median overall survival (OS) and progression free survival (PFS) of 7.5 (95% confidence interval [CI]: 6.6–8.4) and 4.1 (95% CI: 3.7–4.5) months, respectively, in community setting.[5] Single docetaxel use results in 7.5% partial response rate (RR),[6] pemetrexed use in 9.1% RR,[7] and erlotinib use in 8.9% RR.[8] These low survival and RR rates clearly indicate the need to develop more effective therapies for NSCLC after disease progression following first line therapy.

There are now at least 3 immune checkpoint inhibitors that are approved in the second-line setting: nivolumab,[9,10] pembrolizumab,[11] and atezolizumab.[12] Of note, nivolumab and atezolizumab are approved in this setting regardless of the degree of PD-L1 expression while PDL-1 expression >1% is required in the case of pembrolizumab.

### 1.1.1. The Programmed Death 1 (PD-1) Receptor, Its Ligand PD-L1, and a Novel Immunotherapy

An increasing body of evidence, both from lab based animal models and from clinical epidemiology, suggests that the immune system can operate as a significant barrier to tumor formation and progression. One of the hallmarks of cancer is its ability to evade immune destruction.[13] The Programmed death 1 (PD-1) receptor is expressed on activated T- and B-cells.[14] Its major ligand, programmed death ligand 1 (PD-L1) (B7-H1) is typically expressed on a subset of macrophages, but can be induced by inflammatory cytokines in a variety of tissue types, including tumor cells.[15-19] When activated T-cells expressing PD-1 encounter PD-L1, T-cell effector functions are diminished. PD-1 also binds programmed death ligand 2 (PD-L2) (B7-DC), which is expressed selectively on macrophages and dendritic cells.[19-21] These unique expression patterns suggest that PD-L1 promotes self-tolerance in peripheral tissues, while PD-L2 may function in lymphoid organs, although the role of PD-L2 in immunomodulation is not as well understood.[22] Multiple tumor types have been shown to express PD-L1 and PD-L2, effectively co-opting a native tolerance mechanism.[23-26] It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumor tissue may preferentially unleash the cytotoxic function of tumor-specific T cells with fewer

systematic toxic effects than those that are seen with other immune checkpoint inhibitors, such as anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies.[27]

Two large, dose-escalation, phase 1 clinical trials evaluating the safety of the anti–PD-1 antibody nivolumab (formerly known as BMS936558) and the anti–PD-L1 antibody BMS936559 showed significant antitumor activity in subjects with advanced melanoma, lung carcinoma, and renal cell carcinoma, among other cancers, thus validating the PD-1–PD-L1 axis as a therapeutic target.[28-30] Most tumor responses were durable beyond 1 year.[29,30] Toxic effects were generally of low grade. Especially relevant to this protocol, cumulative response rates (all doses) were 18% among patients with non-small-cell lung cancer (14 of 76 patients).[30]

A recent randomized, open-label, phase 3, international study comparing nivolumab to docetaxel in patients with advanced squamous-cell non–small-cell lung cancer who had disease progression during or after first-line chemotherapy showed that OS, PFS and RR were significantly better with nivolumab than docetaxel. The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (hazard ratio, 0.59; 95% CI, 0.44 to 0.79; P<0.001). At 1 year, the OS rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel. The RR was 20% with nivolumab versus 9% with docetaxel (P=0.008). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (hazard ratio for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; P<0.001). Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group.[31]

Pembrolizumab (formerly known as MK-3475) is a highly selective, humanized monoclonal IgG4–kappa isotype antibody against PD-1 that can disrupt the engagement of PD-1 with its ligands and impede inhibitory signals in T Cells, with resultant tumor recognition by cytotoxic T cells. The anti-tumor activity, side effects and safety of pembrolizumab in patients with advanced non-small-cell lung cancer was studied as part of the large, international, Phase 1 KEYNOTE-001 trial. The KEYNOTE-001 trial supported the approval by the U. S. Food and Drug Administration (FDA) of pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. In this trial 495 patients received intravenous (IV) pembrolizumab at a dose of either 2mg or 10mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks over a 30-minute period. The overall RR was 19.4% (95% CI 16.0-23.2), which included a response rate of 18.0% (95% CI, 14.4 to 22.2) in 394 previously treated patients and 24.8% (95% CI 16.7 to 34.3) in the 101 previously untreated patients. The best overall response was stable disease in 21.8% of patients. The RR was similar regardless of dose, schedule and histologic analysis. The median duration of response was 12.5 months (range 1.0 to 23.3) in all patients, 10.4 months (range, 1.0 to 10.4) in previously treated patients and 23.3 months (range, 1.0 to 23.3) in previously untreated patients. Median PFS was 3.7 months (95% CI, 2.9 to 4.1) for all the patients, 3.0 months (95% CI, 2.2 to 4.0) for previously treated patients, and 6.0 months (95% CI, 4.1 to 8.6) for previously untreated patients. Median OS was 12.0 months (95% CI, 9.3 to 14.7) for all the patients, 9.3 months (95% CI, 8.4 to 12.4) for previously treated patients, and 16.2 months (95% CI, 16.2 to not reached) for previously untreated patients.[32] Treatment-related adverse events occurred in 351 patients (70.9%), with no clear difference according to dose or

schedule. The most common treatment-related adverse events were fatigue, pruritus, and decreased appetite. Adverse events of grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related adverse events of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy. Pneumonitis of grade 3 or greater was observed in 9 patients (1.8%), including 1 (0.2%) who died.[32] This study showed durable responses and acceptable tolerance and toxicity profile of pembrolizumab in patients with non-small-cell lung cancer, previously treated as well as untreated patients. It echoed findings from melanoma studies that efficacy and side-effect profile was not significantly different between patients receiving the dose of 10 mg per kilogram every 2 weeks and those receiving 10 mg per kilogram every 3 weeks.

In a recent multicenter study of 135 subjects with advanced melanoma, treatment with MK-3475 was demonstrated to have a high rate of sustained tumor regression with mainly grade 1 or 2 toxicities, and a very low incidence of grade 3 or 4 toxicities.[33] Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to overlap considerably to those obtained with the 2mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be important clinically given that the range of individual exposures is well contained within the range of exposures shown in the melanoma and NSCLC studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

### 1.1.2. Imprime PGG: A Novel Potentiator of Checkpoint Inhibitor Therapy

**Preclinical Mechanism of Action**

Imprime PGG is a 1,3/1,6 β glucan isolated from the cell wall of a proprietary strain of the yeast *Saccharomyces cerevisiae* and is in development for the treatment of cancer in concert with anti-cancer therapeutic antibodies, anti-angiogenics and checkpoint inhibitors.

Imprime PGG is administered intravenously and is bound by naturally occurring anti-β glucan antibodies (ABA) (IgG, IgM) which can then activate complement resulting in the opsonization of the Imprime-ABA complex. This immune complex can then bind directly to innate immune effector cells (macrophages, monocytes, neutrophils) via complement receptor 3 and FcgRIIa (CD32a) and possibly the dectin receptor. Levels of ABA vary in the human population. In healthy human volunteer studies, binding of the Imprime PGG immune complex correlates with higher ABA levels, in particular IgG ABA. These IgG ABA are predominantly

of the IgG2a subtype and interact specifically with the IgG receptor FcgRIIa (CD32a). There are two genetic variants of FcgRIIa – a high binding and a low binding variant- encoded by either the HIS131 or Arg131 alleles, respectively. Imprime PGG binding to, and subsequent activation of, innate immune effector cells is thereby influenced by the levels of ABA and by the affinity of the FcgRIIa. Patients with higher ABA and/ or the high-binding FcgRIIa allele may therefore have the highest likelihood of responding to Imprime PGG- based therapy. A fully qualified ELISA for ABA has been developed. A genetic analysis for the single nucleotide polymorphism at codon 131 has also been developed. Both are being assessed as possible patient selection or stratification markers.[34,35]

Preclinical mechanistic work has revealed that Imprime PGG acts therapeutically as a *Pathogen Associated Molecular Pattern* (PAMP). PAMPs are critical, "non-self" signals efficiently and effectively recognized by the different lineages of the innate immune system-macrophages, monocytes, neutrophils. As a PAMP, Imprime PGG enhances innate immune cell killing, macrophage re-polarization and, importantly, the maturation and activation of professional antigen presenting cells (i.e. dendritic cells). Accordingly, both *ex vivo* research in human whole blood and *in vivo* tumor studies in immunocompetent mice have indicated that Imprime PGG treatment may drive enhanced antigen presentation and cross-talk with T cells, thereby enhancing the efficacy of checkpoint inhibitor therapy. In the syngeneic tumor model MC-38, Imprime PGG treatment significantly expanded the percentage of mice remaining tumor-free from 33% (6/18) in mice treated with αPD-L1 antibody alone to to 83% (14/17) in mice treated with the combination of Imprime PGG and αPD-L1 antibody. Importantly, when re-challenged with MC-38 tumor cells injected on the opposite flank, all of these tumor-free mice remained tumor- free while age-matched, tumor-naïve mice developed tumors. These data provide compelling preclinical evidence that Imprime PGG treatment expanded the percent of mice effectively treated with this checkpoint inhibitor and fostered immunologic memory.[34]

Furthermore, recent work presented at the 2015 American Association for Cancer Research[36] showed that Imprime PGG can modulate PD-L1 expression. Monocytes derived from human whole blood treated with Imprime PGG or vehicle were cultured in media with appropriate cytokines to foster differentiation of macrophages or dendritic cells. Imprime PGG increased the expression of PD-L1 and production of interferon in both macrophages and dendritic cells. When incubated with cell lines from numerous cancer types, including NSCLC, breast, pancreatic, and colon, PD-L1 expression was substantially unregulated on NSCLC, pancreatic and breast cancer cell lines.

Collectively, these preclinical mechanistic studies indicate that Imprime PGG acts as a PAMP to enlist the full functionality of the innate immune system, to generate cross-talk with the adaptive immune system via enhanced antigen presentation and thereby to boost the anti-tumor efficacy of checkpoint inhibitors.

**Clinical Experience to Date**

Clinical benefit of Imprime PGG in NSCLC was demonstrated when Imprime PGG was added to carboplatin, paclitaxel, and cetuximab in a Phase 2 study of 90 patients with previously untreated stage IIIb/IV NSCLC. Patients received cetuximab without or with Imprime PGG 4 mg/kg (2:1 randomization) on Days 1, 8, 15 of each 3-week treatment cycle with carboplatin and paclitaxel on Day 2 of each treatment cycle for the first 4 to 6 cycles. If patients achieved

radiographic stability or response they received cetuximab or cetuximab/Imprime PGG maintenance treatment. Among all evaluable patients, median overall survival was 11.7 months in the control group and 12.4 months in the Imprime PGG group (hazard ratio of 1.04, p=0.90 vs. control). The objective RR (ORR) based on the investigator radiology review of the primary efficacy population was 48% in the Imprime PGG group compared to 23% in the control group (p= 0.047 vs. control). Three-year survival could not be estimated in the control group and was 14% in the Imprime group. Adverse events were consistent with toxicities attributable to the carboplatin, paclitaxel, or cetuximab.[37]

In another multicenter, open-label, international, Phase 2 trial with 92 patients, Imprime PGG in carboplatin and paclitaxel and bevacizumab was compared to chemotherapy and bevacizumab alone in patients with previously untreated stage IIIb/IV non-squamous NSCLC. In 3-week treatment cycles, patients received the standard dose of bevacizumab on Day 1, and standard doses of carboplatin and paclitaxel on Day 2 for 4 to 6 cycles, with or without Imprime PGG 4 mg/kg (2:1 randomization) on Days 1, 8 and 15. Based on central independent radiology review of the primary efficacy population, Imprime PGG improved overall RR by approximately 17% percentage points (60.4% vs 43.5% in control group, p-value 0.2096). The duration of response was increased by 4.7 months in the Imprime PGG group (10.3 months vs 5.6 in control group; p-value 0.940). There was also a trend towards improved PFS (11.6 months in Imprime PGG group vs 9.6 months in control group; p-value 0.5639) and OS (16.1 months in Imprime PGG group vs 11.6 months in control group; hazard ratio 0.66; p-value 0.1345), yielding a 34% reduction in the risk of death. Rates of overall and serious adverse events were similar between groups and were reflective of expected toxicities with the standard of care backbone therapy or complications of patients underlying cancer. The incidence of grade 3 or higher toxicities was higher in the Imprime PGG group overall with no clear preponderance of any specific organ system (93.2% vs 66.7%). Fatal adverse events in the Imprime PGG group were associated with progression of patient's lung cancer. Overall, no significant increase in toxicity with the exception of grade 3/4 neutropenia (39% versus 26.7%) was observed.[38]

**Imprime PGG Dosing Schedule**

After 12 weeks (4 cycles) of weekly dosing of Imprime PGG during Phase II, the compound will be administered on a 3-weekly schedule coinciding with and preceding the administration of pembrolizumab on the first day of each cycle. The change to q3wk dosing during the Phase II aligns with the q3wk dosing of pembrolizumab and will follow two response assessments by RECIST v1.1 (CTs will be done prior to initiation of dosing at Cycle 3 and Cycle 5). Previous clinical experience with Imprime PGG in NSCLC indicate that most observed clinical responses have occurred within the first 12 weeks of dosing. There are no concerns that this change would negatively impact patient safety. This change is intended to explore whether parameters of innate immune responses (cytokines, chemokines, myeloid cell mobilization, complement activation, etc.) are maintained on a 3-week schedule with maintenance of clinical benefits in a more conveniently manageable clinical schedule.

### 1.2. Study Rationale

There is recent convincing evidence that anti-PD-1 antibodies, like pembrolizumab, have efficacy in treating NSCLC. Imprime PGG improved the overall response rates and improved trends towards PFS and overall survival when given in conjunction with standard of care NSCLC therapy. Imprime PGG also increased PD-L1 expression in NSCLC cell lines. In addition, preclinical mechanistic studies have revealed that Imprime PGG acts as a PAMP to enlist the full functionality of the innate immune system, enhancing dendritic cell maturation and antigen presentation and eliciting T cell expansion to boost the anti-tumor efficacy of checkpoint inhibitors. The present study is an exploratory single-arm study consisting of a dose escalation Phase 1b component and a Phase 2 component for combination therapy of pembrolizumab and Imprime PGG. The primary endpoint for the Phase Ib component is the maximum tolerated dose (MTD) of Imprime PGG in combination with pembrolizumab. For the Phase II component of the study, based upon the scientific evidence for Imprime PGG's therapeutic effect, we hypothesize that addition of Imprime PGG to pembrolizumab will enhance therapeutic responses to pembrolizumab in second line setting of NSCLC.

## 2. OBJECTIVES

### 2.1. Phase Ib Objectives

#### 2.1.1. Primary Objective

The primary objective of the Phase Ib dose escalation cohort study is to establish the maximum tolerated dose (MTD) of Imprime PGG in combination with pembrolizumab for subjects with metastatic non-small cell lung cancer (NSCLC) after progression on first-line platinum-based chemotherapy.

#### 2.1.2. Secondary Objectives

- Characterize adverse effects (AE) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line platinum-based chemotherapy.
- Estimate clinical benefit rate (CBR: complete response, partial response, or stable disease) as measured by RECIST v1.1 of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line platinum-based chemotherapy.
- Estimate Progression-Free Survival (PFS) and 6-month PFS using RECIST v1.1 in subjects with NSCLC who progressed after first-line platinum-based chemotherapy when treated with Imprime PGG in combination with pembrolizumab.
- Estimate overall survival (OS) and 1-year OS in subjects with NSCLC who progressed after first-line platinum-based chemotherapy when treated with Imprime PGG in combination with pembrolizumab.

#### 2.1.3. Correlative Objectives

- Correlate biomarkers on immune cell subsets (including, but not limited to monocytes, macrophages, granulocytes, and lymphocytes, and PD-L1) concentrations and localization (peri- vs. intratumoral) in archived diagnostic tumor tissue with PFS and CBR.
- Correlate change in soluble PD-L1 levels pre-dose Cycles 2 and 3, relative to baseline (i.e., pre-dose Day 1 of Cycle 1) level with PFS and CBR.
- Correlate PD-L1 expression on circulating peripheral mononuclear cells from whole blood pre-dose Cycles 2 and 3, relative to baseline (i.e., pre-dose Day 1 of Cycle 1) level.

- Correlate baseline (i.e., pre-dose Day 1 of Cycle 1) anti-β-glucan antibody (ABA) (IgM, IgG) levels in serum with PFS and CBR.
- Correlate baseline immune classifiers with PFS and CBR.
- Correlate FcγRIIa polymorphism to PFS and CBR.

## 2.2. Phase II Objectives

### 2.2.1. Primary Objective

The primary objective of the Phase II trial is to estimate Progression-Free Survival (PFS) using RECIST v1.1 in subjects with metastatic non-small cell lung cancer (NSCLC) treated with Imprime PGG in combination with pembrolizumab after progression on first-line systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy).

### 2.2.2. Secondary Objectives

- Characterize adverse effects (AE) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line systemic therapy.
- Estimate clinical benefit rate (CBR: complete response, partial response, or stable disease) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line systemic therapy.
- Estimate Progression-Free Survival (PFS) and 6-month PFS using RECIST v1.1 in subjects with NSCLC when treated with Imprime PGG in combination with pembrolizumab who progressed after first-line systemic therapy.
- Estimate overall survival (OS) and 1-year OS in subjects with NSCLC treated with Imprime PGG in combination with pembrolizumab who progressed after first-line systemic therapy.

### 2.2.3. Correlative Objectives

- Correlate biomarkers on immune cell subsets (including, but not limited to monocytes, macrophages, granulocytes, and lymphocytes, and PD-L1) concentrations and localization (peri- vs. intratumoral) in archived diagnostic tumor tissue with PFS and CBR.
- Correlate change in soluble PD-L1 levels pre-dose Cycles 2 and 3, relative to baseline (i.e., pre-dose Day 1 of Cycle 1) level with PFS and CBR.
- Correlate PD-L1 expression on circulating peripheral mononuclear cells from whole blood pre-dose Cycles 2 and 3, relative to baseline (i.e., pre-dose Day 1 of Cycle 1) level.
- Correlate anti-β-glucan antibody (ABA) (IgM, IgG) levels in serum with PFS and CBR.
- Correlate baseline immune classifiers with PFS and CBR.
- Correlate FcγRIIa polymorphism to PFS and CBR.

# 3. ELIGIBILITY CRITERIA

Study entry is open to adults regardless of gender or ethnic background. While there will be every effort to seek out and include women and minorities, the subject population is expected to be no different than that of other advanced solid tumor cancer studies at each participating institution.

## 3.1. Inclusion Criteria

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

1. Male or female ≥ 18 years of age at time of consent.
2. Subjects with histologically or cytologically confirmed non-small cell lung cancer (NCSLC).
3. Subjects with stage IV non-small cell lung cancer as defined by American Joint Committee on Cancer (AJCC) 7th Edition. Patients with locally advanced or recurrent disease who are candidates for systemic therapy are also allowed.
4. Subjects without EGFR activating mutation (Exon 19 del, L858R) or ALK, ROS translocation if histology is adenocarcinoma. Subjects with an EGFR activating mutation or ALK translocation are eligible only after failing TKI therapy (such as gefitinib, erlotinib, or afatinib). Furthermore, if a T790M resistance mutation is found, the patient must have failed a 3rd generation TKI such as osimertinib
5. Phase Ib: Subjects who progressed after first-line platinum-based chemotherapy and who are candidates for second-line therapy.
   Phase II: Subjects who have progressed on first-line systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy) who are candidates for second-line systemic therapy. Patients with early stage cancer will also be eligible if progression occurs:
   a. within 6 months of adjuvant chemotherapy after curative resection
   b. within 6 months of adjuvant chemotherapy after curative resection while on adjuvant immunotherapy, currently only available as part of a clinical trial
   c. within 6 months of curative surgery if chemotherapy is given in the neoadjuvant setting
   d. within 6 months of completion of chemoradiation (or 6 months from completion of consolidation chemotherapy if administered after concurrent chemoradiation)
   e. within 6 months of completion of chemoradiation or consolidation chemotherapy (if administered) while on consolidation immunotherapy, a setting for which durvalumab is FDA approved.

   Phase II: Subjects with an EGFR or ALK mutation who are no longer candidates for TKI therapy and have progressed on standard systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy).
6. Phase II only: Measurable disease according to RECIST v1.1 (Section 8) obtained by imaging within 28 days prior to study registration. Phase Ib: subjects may enroll with or without measurable disease.
7. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 within 28 days prior to study registration.
8. Life expectancy of 6 months or greater as determined by the treating physician.
9. Adequate hepatic function within 28 days prior to study registration defined as meeting **all** of the following criteria:
   - total bilirubin ≤ 1.5 × upper limit of normal (ULN) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN (except subject with Gilbert's Syndrome, who can have total bilirubin < 3.0 mg/dl)

- aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
- alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases

10. Adequate renal function within 28 days prior to study registration defined by **either** of the following criteria:
    - Serum creatinine ≤ 3 mg/dL
    - if serum creatinine > 3mg/dL, estimated glomerular filtration rate (GFR) ≥ 20 mL/min
11. Adequate hematologic function within 28 days prior to study registration defined as meeting **all** of the following criteria:
    - hemoglobin ≥ 9 g/dL; subjects requiring transfusion will be eligible to start study
    - and absolute neutrophil count (ANC) ≥ $1.5 \times 10^9$/L
    - and platelet count ≥ $100 \times 10^9$/L
12. Adequate coagulation functioning within 28 days prior to study registration defined by **either** of the following criteria:
    - INR < 1.5 × ULN
    - for subjects receiving anticoagulant, the subjects must, in the investigator's opinion, be clinically stable with no evidence of active bleeding while receiving anticoagulant therapy. The INR for subjects on warfarin should be in the therapeutic range. Low molecular weight heparin (LMWH) is allowed.
13. Provided written informed consent and HIPAA authorization for release of personal health information, approved by an Institutional Review Board (IRB).
    **NOTE**: HIPAA authorization may be included in the informed consent or obtained separately.
14. Women of childbearing potential (WOCP) must not be pregnant or breast-feeding. A negative serum or urine pregnancy test is required within 72 hours of study registration. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required.
15. Women of childbearing potential (WOCP) must be willing to use two effective methods of birth control such as an oral, implantable, injectable, or transdermal hormonal contraceptive, an intrauterine device (IUD), use of a double barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream), or total abstinence for the course of the study until 120 days after the last dose of study drug.
    **NOTE**: Women are considered to be of childbearing potential unless they are postmenopausal (≥45 years of age and has not had menses for greater than 12 consecutive months), surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or not heterosexually active for the duration of the study and at least 120 days after the last dose of study drug.
16. Men who are not surgically sterile (vasectomy) must agree to use an acceptable method of contraception. Male subjects with female sexual partners who are pregnant, possibly pregnant, or who could become pregnant during the study must agree to use condoms from the first dose of study drug through at least 120 days after the last dose of study drug. Total abstinence for the same study period is an acceptable alternative.
17. Willingness and ability to comply with scheduled visits (including geographical distance), treatment plans, laboratory tests, and other study procedures.

### 3.2. Exclusion Criteria

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

1. Surgery within 4 weeks prior to study registration except for minor procedures.
   **NOTE**: Hepatic biliary stent placement, PleurX catheter, port placement, ureteral stent or other minor surgeries are allowed. **NOTE**: Subject must have adequately recovered from the toxicity

and/or complications of major surgery prior to study registration, as determined by the treating physician.

2. Patients with known untreated or active central nervous system (CNS) metastases. Subjects suspected to have brain mets should undergo brain MRI (or CT head if MRI is not feasible) to exclude brain metastases. Patients with treated brain metastases will be eligible as long as their symptoms are improving or achieved new baseline and not requiring steroids for at least 2 weeks. Patients with leptomeningeal disease will be excluded regardless of clinical stability.
3. Previously received a solid organ transplant or allogeneic progenitor/stem cell transplant.
4. Received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
5. History of blood clots, pulmonary embolism, or deep vein thrombosis unless on adequate anticoagulant therapy as determined by the treating investigator (subject must be on stable dose for 2 weeks) and all symptoms have resolved.
6. Known history of human immunodeficiency virus [(HIV) HIV 1/2 antibodies].
7. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
8. Current use of immunosuppressive medication at time of study entry. The following are exceptions to this exclusion criterion: intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); steroids as premedication for hypersensitivity reactions (eg, CT scan premedication). Cases requiring systemic corticosteroids at physiologic doses must be discussed with Big Ten CRC and HiberCell prior to enrollment.
9. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Exceptions include: patients with controlled diabetes type 1, controlled hypo- or hyperthyroidism, resolved childhood asthma/atopy, vitiligo, or psoriasis not requiring immunosuppressive treatment.
10. Received prior chemotherapy, an immune checkpoint inhibitor, or radiation therapy within 2 weeks prior to study registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events from previously administered agents.
    **NOTE**: Subjects with alopecia, lymphopenia, grade ≤ 2 sensory neuropathy or other grade ≤ 2 AEs not constituting a safety risk based on investigator judgement are an exception to this criterion and can still be considered for the study.
11. Any clinically significant or active infection requiring anti-infective treatment. Patients with infection that is adequately treated will be eligible.
12. History of interstitial lung disease requiring immunosuppressive/steroids or history of immunotherapy related pneumonitis that has required steroids or immunosuppression in the past
13. Known history of active tuberculosis.
14. Any other severe, uncontrolled medical condition, including uncontrolled diabetes mellitus (defined as a Hemoglobin A1C ≥ 9% in subjects with a prior history of diabetes, 28 days prior to study registration) or unstable congestive heart failure (Stage III-IV of the New York Heart Association Functional Classification)
15. Previous known allergy or intolerance to pembrolizumab or any of its excipients
16. Previous exposure or known allergy to Imprime PGG or any of its excipients
17. Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies

18. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, interfere with protocol compliance, or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for enrollment in this study.
19. Presence of any non-healing wound, fracture, or ulcer within 28 days prior to study registration.
20. Any mental or medical condition that prevents the subject from giving informed consent or participating in the trial.
21. No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, in situ breast cancer, Gleason ≤ grade 7 prostate cancers, low grade papillary urothelial carcinoma or other cancer for which the subject has been disease-free for at least 2 years. And no additional therapy other than hormonal therapy is required or anticipated to be required during the trial period.
22. Treatment with any therapeutic investigational agent within 28 days prior to study registration.

# 4. SUBJECT REGISTRATION

All subjects must be registered through BTCRC Administrative Headquarters' electronic data capture (EDC) system. A subject is considered registered when an 'On Study' date is entered into the EDC system. A subject is considered registered when an 'On Study' date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy.

# 5. OVERALL DESIGN AND TREATMENT PLAN

## 5.1. Phase Ib Dose Escalation Study

This Phase Ib dose escalation study will evaluate pembrolizumab in combination with Imprime PGG in subjects with metastatic NSCLC after failure of first-line platinum-based chemotherapy. Imprime PGG will be given on Day 1, 8 and 15 and pembrolizumab will be given on Day 1 of each 21-day cycle. Treatment will continue until disease progression, unacceptable toxicity, subject refusal, or subject death either from progression of disease, the therapy itself, or from other causes, or completion of 16 cycles of treatment. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for up to 5 years from the start of study medication.

| Dose Cohort | # of Subjects | Imprime PGG | Pembrolizumab (mg) |
|---|---|---|---|
| 1 | 3-6 | 2 mg/kg | 200 |
| 2 | 3-6 | 4 mg/kg | 200 |

### 5.1.1. Dose Escalation Rules and MTD Definition

- Three to six subjects will initially be enrolled at dose level 1. If none of the 3 subjects experience a dose limiting toxicity (DLT) during the first cycle of therapy, an additional three subjects will be enrolled at dose level 2. If all subjects in dose level 2 complete the first cycle of therapy without DLT, 3 more subjects will be enrolled into dose level 2 to

ensure only 0-1 of 6 subjects have a DLT. There will be no further escalation beyond dose level 2.

- Alternatively, if 1 of the first 3 subjects within a dose level cohort experiences a DLT, the cohort will be expanded to 6 subjects. If this happens within dose level 1 and only 1 of the total 6 subjects in dose level 1 experience DLT, the study will proceed to dose level 2. If 2 or more of 6 subjects in a cohort experience DLTs, or 2 subjects within a cohort of 3 subjects experience DLT during the first cycle of therapy (>33% of subjects experiencing DLT), the MTD is exceeded. If this occurs at dose level 2, 3 additional subjects will be enrolled into dose level 1, unless there have been 6 subjects already enrolled into dose level 1.

- The maximum tolerated dose of Imprime PGG in combination with pembrolizumab is the highest tested dose of Imprime PGG combined with pembrolizumab with DLT rate of less than 33% in first cycle of therapy (i.e., ≤1 out of 6 subjects with DLT). That dose will be recommended for the Phase II study.

- At the discretion of the sponsor-investigator, a lower phase II dose may be recommended if other toxicity emerges during the Phase Ib study which does not meet DLT criteria but limits the dose that can be administered cumulatively.

5.1.2. **Definition of Dose Limiting Toxicity**

Dose limiting toxicity (DLT) is defined as one of the following events occurring during cycle 1:

- Grade 3 or greater treatment-related **excluding**:
  - Grade 3-4 nausea and/or vomiting that resolves in 72 hours.
  - Grade 3-4 laboratory abnormalities that are not clinically significant and which resolve in 72 hours.
  - Grade 3 fatigue lasting < 5 days.
- Delay of cycle 2 treatment start by more than 2 weeks due to unresolved treatment related grade 3 or greater non-hematologic toxicity.

DLTs will be counted based on the number of subjects with DLT at a given dose level, not the absolute number of DLTs. No single subject can trigger more than one DLT event.

Additional subject cohorts will not be enrolled at the second dosing level until all subjects at the initial dosing level complete all planned treatment for cycle 1 (defined as 1 dose of pembrolizumab, and 3 doses of Imprime PGG) and are able to start cycle 2 with no more than a 2-week delay.

Intra-subject dose escalation is not permitted.

Once the maximum tolerated dose of pembrolizumab in combination with Imprime PGG is determined, enrollment will continue until at least 6 subjects total are accrued at the maximum tolerated dose.

### 5.2. Phase II Study

The primary objective of the Phase II trial is to determine the activity of the combination of pembrolizumab and Imprime PGG in second line therapy for subjects with NSCLC as assessed by progression-free survival (PFS). Pembrolizumab will be given on Day 1 of each 21 day cycle after Imprime PGG, and the RP2D dose of Imprime PGG will be given on Days 1, 8 and 15 for Cycles 1-4, and on Day 1 only for Cycles 5-16 of each 21 day cycle. Treatment will continue up to 16 cycles, or until disease progression, unacceptable toxicity, subject refusal, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for a total of 5 years.

### 5.3. Correlative Research (all phases)

Correlative research analyses include examining the relationship between clinical response at the end of Cycle 2 (Week 6) with biomarkers on immune cell subsets (including, but not limited to monocytes, macrophages, granulocytes, and lymphocytes, and PD-L1) concentrations and localization (peri- vs. intratumoral) in archived diagnostic tumor tissue with PFS and CBR. Research analyses also include examining the relationship between changes in soluble PD-L1 level and PD-L1 expression on circulating mononuclear cells at baseline (i.e., pre-dose Day 1 of Cycle 1) and during therapy (assessed pre-dose on Day 1 of Cycles 2 and 3) and correlated with PFS and to CBR. Additionally, baseline immune classifiers, FcγRIIa polymorphism, and anti-β-glucan antibody (ABA) (IgM, IgG) levels will be correlated with PFS and CBR.

### 5.4. Imprime PGG Pre-medication

Each cycle will be 3 weeks in duration. The most common adverse events leading to treatment discontinuation of Imprime PGG in clinical trials as of the Imprime PGG Investigator's Brochure Edition 10 (October 29, 2014) included infusion related reactions/hypersensitivity (rash, nausea, dyspnea, tachycardia, urticaria, hypersensitivity). In addition, in a trial comparing Imprime PGG in combination with bevacizumab and concomitant paclitaxel and carboplatin (BPC) versus the BPC chemotherapy combination without Imprime PGG, events potentially associated with hypersensitivity reactions occurred more frequently in the Imprime PGG arm. These included one grade 3 event of anaphylactic reaction deemed related to Imprime PGG. Based on this, Imprime PGG premedication is recommended, but not mandated. Subjects may receive pre-medication as outlined below before dosing of Imprime PGG on each treatment day and as needed post-dosing.

- Cycle 1/Day 1: Pretreat with an H1 antagonist (e.g., 25- 50 mg of diphenhydramine PO or IV) along with ranitidine (or equivalent) 50 mg IV or 150 mg PO.
- Subsequent cycles: Premedication is allowed but preferably would be at reduced doses of those used at Cycle 1 Day 1.

## 5.5. Drug Administration

### 5.5.1. Table 1 Phase Ib Imprime PGG + Pembrolizumab Administration:

| Drug | Administration Sequence | Dose[1] | Length and route of administration | Frequency of administration | Length of cycle |
|---|---|---|---|---|---|
| Imprime PGG | 1st | 2 mg/kg<br>4 mg/kg | 2-4 hours[2]; IV | Day 1, 8, 15 | 21 days |
| Pembrolizumab | 2nd (15-30 minutes post Imprime PGG) | 200 mg | 30-min (-5/+10); IV | Day 1 | |

[1]Dose of Imprime PGG for phase Ib varies dependent on dose cohort; either 2 or 4mg/kg will be used for phase II.
[2]Length of infusion for Imprime PGG will vary dependent on dose and subject's weight (See section 10 for additional information).

Phase Ib: Dosing will occur in 21-day cycles. Imprime PGG in the Phase Ib dose escalation study will be dosed at 2 mg/kg IV or 4 mg/kg IV on Day 1, 8, and 15 of the 21 day cycle. On day 1 of each cycle, the Imprime PGG intravenous infusion is given first followed 15-30 minutes later by the pembrolizumab infusion. Imprime PGG will be administered as a 2-4 hour intravenous infusion, based on dose and the subject's weight. Extended infusion times are acceptable and will not incur a deviation; the rate of infusion should not be increased. See section 10 and the Imprime PGG Pharmacy Manual.

Pembrolizumab will be administered as a 30-minute intravenous infusion. Given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

### 5.5.2. Table 2 Phase II Imprime PGG + Pembrolizumab Administration:

| Drug | Administration Sequence | Dose[1] | Length and route of administration | Frequency of administration | Length of cycle |
|---|---|---|---|---|---|
| Imprime PGG | 1st | At RP2D (4mg/kg) | 2-4 hours[2]; IV | Cycles 1-4: Day 1, 8, 15<br>Cycles 5-16: Day 1 | 21 days |
| Pembrolizumab | 2nd (15-30 minutes post Imprime PGG) | 200 mg | 30-min (-5/+10); IV | Day 1 | |

[1]Dose of Imprime PGG for phase Ib varies dependent on dose cohort; For phase II, Imprime PGG dose will be 4mg/kg as determined by phase Ib part of the study; RP2D = Recommended Phase 2 Dose.
[2]Length of infusion for Imprime PGG will vary dependent on dose and subject's weight (See section 10 for additional information).

Phase II: Imprime PGG will be dosed at the dose established as the MTD in Phase Ib (4mg/kg) on Day 1, 8, and 15 for Cycles 1-4, and on Day 1 only for Cycles 5-16 of the 21 day cycle. Pembrolizumab will be infused at 200 mg on Day 1 of the 21 day cycle. On day 1 of each cycle, the Imprime PGG intravenous infusion is given first followed 15-30 minutes later by

the pembrolizumab infusion. Imprime PGG will be administered as a 2-4 hour intravenous infusion, based on dose and the subject's weight. Extended infusion times are acceptable and will not incur a deviation; the rate of infusion should not be increased. See section 10 and the Imprime PGG Pharmacy Manual.

Pembrolizumab will be administered as a 30-minute intravenous infusion. Given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Subsequent cycles must meet the criteria found in section 6.1 and may begin 1 day earlier or up to 2 days later to accommodate scheduling issues.

For All Phases of Study:

- Please note that the infusion timeline is approximate and may vary depending on the individual subject (weight and reaction to former treatment with study drugs may alter length of treatment and monitoring).

- The Imprime PGG dose should be recalculated if the subject's weight changes by ≥ 10%.

5.5.3. **Monitoring:**

- Vital signs including blood pressure, pulse, temperature, respirations, and pulse oximetry, will be measured as follows:
  - Imprime PGG infusion: prior to infusion, every 2 hours during infusion (±15 min), and within 30 minutes of the completion of the Imprime PGG infusion (and prior to pembrolizumab infusion).
  - Pembrolizumab infusion: prior to infusion (NOTE: this can be same as the post Imprime PGG infusion timepoint) and within 10 minutes of infusion completion.
- Subjects will be closely monitored for toxicities. Toxicity will be assessed using CTCAE version 4.

## 5.6. Supportive Care

Optimal care should be given to all subjects.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. If prophylactic antiemetic therapy is needed, 5-HT3 receptor antagonists (without corticosteroids) should be tried first. Due to the potential of benzodiazepines to cause sedation, the use of benzodiazepines for antiemetic prophylaxis should be reserved for subjects who cannot be satisfactorily managed otherwise. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Although acetaminophen at doses of ≤2 grams/day is permitted, it should be used with caution in subjects with impaired liver function.

#### 5.6.1. Pembrolizumab Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Table 4.

Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

**NOTE**: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined in Table 4).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

## 5.7. Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor-investigator by contacting the BTCRC Project Manager. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

#### 5.7.1. Permitted Concomitant Medications and Procedures

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the electronic case report form (eCRF).

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered beyond 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 11.

Myeloid growth factors to treat subjects with neutropenia according to the American Society of Clinical Oncology (ASCO) Guidelines are permitted. Myeloid growth factors should be avoided (if medically appropriate) in Cycle 1 until subjects have developed a DLT or dose-limiting Grade 4 neutropenia.

Antiemetic agents may be administered at the discretion of the investigator but are not commonly required as a prophylactic agent. All other manifestations of the subject’s malignancy should be treated at the discretion of the investigator.

Medications with potential CNS effects are not prohibited in this study, but it is recommended that their use be minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with pembrolizumab and Imprime PGG.

In appropriate settings, such as combinations with agents known to produce frequent thrombocytopenia, restricted uses of anticoagulants should be considered.

All other medical conditions should be treated at the discretion of the investigator in accordance with local community standards of medical care.

5.7.2. **Prohibited Concomitant Medications**

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Concomitant use of chemotherapy
- Investigational agents other than Imprime PGG
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with sponsor-investigator via the BTCRC Project Manager.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor-investigator via the BTCRC Project Manager.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

## 5.8. Diet/Activity/Other Considerations

**Diet**

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

**Contraception:**

Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

It is not known if Imprime PGG has adverse effects on a fetus *in utero* nor if there are adverse effects on the composition of sperm.

Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 12 consecutive months), or 3) not heterosexually active for the duration of the study and at least 120 days after the last dose of study drug. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from the first study visit, throughout the study period, and up to 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirements described above for the duration of the study and 120 days following the last dose of study drug. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

**Use in Pregnancy:**
If a subject inadvertently becomes pregnant while on study, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to BTCRC Administrative Headquarters (AHQ) immediately and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to BTCRC AHQ. BTCRC AHQ will report the event to Merck and HiberCell.

If a male subject impregnates his female partner, he must immediately inform the site study personnel and the pregnancy reported to BTCRC AHQ and to Merck and followed as described above and in Section 11. BTCRC AHQ will report the event to Merck and HiberCell.

**Use in Nursing Women:**
It is unknown whether pembrolizumab or Imprime PGG is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

# 6. DOSE DELAYS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of protocol therapy.

## 6.1. Start of a New Cycle

A new treatment cycle will only be initiated when all of the following conditions are met:

- ANC $\geq$ 1,000$\times$ $10^9$/L
- platelets $\geq$ 80 $\times$ $10^9$/L
- non-hematologic treatment related $\geq$ grade 3 toxicities need to improve to either $\leq$ Grade 1 or as specified in table 4 or to the subject's baseline values (except alopecia)

If toxicities are outside the acceptable threshold, the subject should be assessed weekly (phone or clinic) until toxicities are at an acceptable level. Missed doses will not be made up. If treatment is unable to restart within 12 weeks of the planned treatment date, the subject will be permanently discontinued from study therapy (both pembrolizumab and Imprime PGG should be stopped).

**NOTE**: For cycle 1 only, the inability to start cycle 2 within 2 weeks of the planned date is a DLT; however, the subject is allowed an additional week of recovery and is allowed to remain on study if treatment restarts within 12 weeks.

## 6.2. Management of Allergic Reaction/ Hypersensitivity

### 6.2.1. **Imprime PGG**

In case of severe adverse events during infusion of Imprime PGG, the infusion may be interrupted at the discretion of the treating physician for 30-60 minutes and restarted when the adverse event has resolved. Alternatively, the infusion rate may be decreased by 50% instead of, or after, interruption at the discretion of the treating physician. Management of adverse events should include treatments as indicated by symptoms.

An appropriate resuscitation plan should in place and a physician readily available during the period of drug administration.

### 6.2.2. **Pembrolizumab**

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

**Table 3** provides treatment guidelines for subjects who experience an infusion related reaction associated with administration of pembrolizumab.

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | None |
| Grade 2<br>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.** | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:<br><br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br><br>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |
| Grades 3 or 4<br><br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br><br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine**<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**Subject is permanently discontinued from further trial treatment administration.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration. | | |

## 6.3. Other Adverse Event Guidelines

If treatment is delayed longer than 12 weeks, the subject will be discontinued from study treatment (both pembrolizumab and Imprime PGG should be stopped).

## 6.4. Dose Modifications

### 6.4.1. **Pembrolizumab Dose Modifications**

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4 below.

**Table 4: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab.**

**General instructions:**

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

| Immune-related AEs | Toxicity grade or conditions (CTCAEv4.0) | Action taken to pembrolizumab | irAE management with corticosteroid and/or other therapies | Monitor and follow-up |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment<br>• Add prophylactic antibiotics for opportunistic infections |
| | Grade 3 or 4, or recurrent Grade 2 | Permanently discontinue | | |
| Diarrhea / Colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).<br>• Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.<br>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. |
| | Grade 4 | Permanently discontinue | | |
| AST / ALT elevation or Increased bilirubin | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable |
| | Grade 3 or 4 | Permanently discontinue | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | |

| | | | | |
|---|---|---|---|---|
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer anti-hyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes. |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated. | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders. |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care | • Monitor for signs and symptoms of thyroid disorders. |
| Nephritis and Renal dysfunction | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Grade 1 or 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| All other immune-related AEs | Intolerable/ persistent Grade 2 | Withhold | • Based on type and severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis | | |
| | Gr. 4 or recurrent Gr. 3 | Permanently discontinue | | |

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
**NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

## Other allowed dose interruption for pembrolizumab

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the BTCRC Project Manager. The reason for interruption should be documented in the subject's study record.

# 7. STUDY CALENDAR & EVALUATIONS [Cycle = 21 days]

| Study Day | Screen | **All Phases:** Cycle 1-4[4] (±3) | | | **Phase Ib:** Cycle 5-16 | | | **Phase II:** Cycle 5-16 | Every 2/3 cycles | Safety Follow Up | Long-term Follow Up (±14) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | -28 days | Day 1[4] | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 (± 3) | C 3, 5, etc. Day 1 (±7) | 30 days (±7) post last dose | Q3 mos for 1 yr; Q6 mos for yrs 2-5 |
| **REQUIRED ASSESSMENTS** | | | | | | | | | | | |
| Informed Consent/ HIPAA auth. | X | | | | | | | | | | |
| Medical Hx: prior Tx, pathology, trial awareness question | X | | | | | | | | | | |
| Substance use: smoking history (amt, freq, start/stop) | X | | | | | | | | | | |
| Physical examination, height (screen only), weight | X | X | | | X | | | X | | X | |
| Vital Signs (BP, pulse, temp, resp. and pulse ox. See 5.5.3) | X | X | X | X | X | X | X | X | | X | |
| ECOG performance status | X | X | C1[9] | C1[9] | X | | | X | | X | |
| Blood Chemistries[1] | X | X | C1[9] | C1[9] | X | | | X | | | |
| Thyroid Function (TSH, T3, T4) | X | C2-4 | | | X | | | X | | | |
| PT/INR and aPTT | X | C1 | C1[9] | C1[9] | | | | | | | |
| Platelets, ANC & Hgb | X | X | C1[9] | C1[9] | X | | | X | | | |
| Urinalysis | X | X | C1[9] | C1[9] | X | | | X | | | |
| Pregnancy test for WOCP[6] | -72h | | | | | | | | | | |
| AE, ECI and irAE assessment | X | X | C1[9] | C1[9] | X | | | X | | X[5] | |
| Concomitant medications | X | X | C1[9] | C1[9] | X | | | X | | X | |
| Survival | | | | | | | | | | | X |
| **DISEASE ASSESSMENT** | | | | | | | | | | | |
| CT chest, abdomen/pelvis | X[2] | | | | | | | | X[2] | | X[10] |
| CT or MRI Brain, if indicated. See Section 3.2.2. | [X] | | | | | | | | | | |
| **TREATMENT** | | | | | | | | | | | |
| Imprime PGG | | X | X | X | X | X | X | X | | | |
| Pembrolizumab | | X | | | X | | | X | | | |
| **CORRELATIVE STUDIES** | | | | | | | | | | | |
| Unstained slides from archived tumor tissue[3] | | C1 | | | | | | | | | |
| Whole blood for soluble PD-L1and PBMCs | | C1-3[7] | | | | | | | | | |
| Blood for FcγRIIa polymorphism | | C1[8] | | | | | | | | | |
| **Phase Ib**: Blood for ABAs (Imprime)[11] | | C1 | | | | | | | | | |
| **Phase II**: Blood for ABAs (Imprime) pre/post infusion[11] | | C1-3 | | | | | | C5, 6, 7 | | | |
| Blood for immune classifiers | | C1[8] | | | | | | | | | |
| **BANKINGSAMPLES** | | | | | | | | | | | |
| Whole Blood[12] | | C1 | | | | | | | | | |
| Unstained slides from archived tumor tissue[13] | | C1 | | | | | | | | | |
| Serum and plasma[14] | | C1 | | | | | | | | X | |

Footnotes:

1: Blood Chemistries to include: sodium, potassium, serum creatinine (or GFR; see 3.1.11), calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein

2: Appropriate scans to assess disease status will be obtained within 28 days of study registration including CT chest, abdomen/pelvis. CT pelvis is only required if there are known pelvic mets. During treatment, scans to assess disease status will be done every 2 cycles, starting within one week before Cycle 3 Day 1. If the subject has achieved at least stable disease after 7 cycles, disease assessment may be performed every 3 cycles thereafter until disease progression.

3: Submission of unstained slides from archived tumor tissue for (1) evaluation of concentrations and localization (peri- vs. intra-tumoral) of biomarkers on immune cell subsets (including monocytes, macrophages, granulocytes, and lymphocytes) and (2) evaluation of expression of PD-L1are to be submitted after the subject is registered to the trial. These must be submitted prior to Cycle 2. If archived tumor tissue is not available, the subject does not need to undergo a biopsy to obtain tissue. See CLM for collection, labeling and shipping instructions.

4: For cycle 1 only: labs do not need to be repeated if done within 7 days of day 1. All infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. This should be clearly documented in subject's chart and case report forms.

5: For subjects with unresolved treatment related toxicity, follow as medically appropriate until resolution or stabilization

6: A negative serum or urine pregnancy test is required within 72 hours of study registration. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required.

7: Whole blood for serum (soluble PD-L1 level, PD-L1 expression on circulating mononuclear cells analyses) will be collected before drug treatment on Day 1 of Cycles 1, 2, and 3. See CLM for collection, processing, labeling and shipping instructions.

8: Whole blood for serum (FcγRIIa polymorphism and immune classifiers) will be collected before drug treatment on Day 1 of Cycle 1. See CLM for collection, processing, labeling and shipping instructions.

9: **Phase Ib only**: To be performed weekly (Days 1, 8, and 15) during Cycle 1 (DLT evaluation period).

10: Disease assessment will be performed every 6-months for subjects who did not progress during treatment

11: **Phase Ib**: Whole blood for serum ABA analyses will be collected before study drugs on Day 1 of Cycle 1.
**Phase II**: Whole blood for serum ABA (Imprime) and other immune correlates. Subjects will have ABAs collected pre/ post Imprime PGG infusion at: Cycles 1, 2, 3, 5, 6, and 7.

12: Submission of whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.

13: Submission of unstained slides for banking from an archived FFPE tumor block is requested. See CLM for collection, labeling, and shipping instructions.

14: Submission of serum and plasma for banking are to be collected at Pre-Treatment Cycle 1 Day 1 and at the Safety Follow Up visit. See CLM for collection, labeling, processing, and shipping instructions.

## 7.1. Screening Evaluations

### 7.1.1. Within 28 days prior to study registration

- Informed consent, HIPAA authorization
- Medical history including prior therapies, pathology and trial awareness question.
- Substance use: smoking history. To include: amount, frequency, start and stop dates of cigarette, cigar and pipe usage.
- Physical exam, height (screening only), weight
- Vital signs (blood pressure, heart rate, temperature)
- ECOG performance status
- Blood chemistries (sodium, potassium, serum creatinine [or GFR; see 3.1.11], calcium, albumin, ALT, AST, bilirubin, alkaline phosphatase, total protein)
- Thyroid function (TSH, T3, T4). T3, T4: free or total as per local standards.
- PT/INR and aPTT
- Platelets, ANC and hemoglobin
- Urinalysis
- Baseline signs and symptoms
- Concomitant medications
- CT chest, abdomen, pelvis. CT pelvis is only required if there are known pelvic mets.
- CT or MRI of brain, if indicated. See Section 3.2.2.

### 7.1.2. Within 72 hours prior to study registration

- Pregnancy test for women of childbearing potential (WOCP). A negative serum or urine pregnancy test is required within 72 hours of study registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

## 7.2. On Treatment (±3)

### 7.2.1. Cycle 1 Day 1:

**Note:** Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical exam, weight
- Vital signs (blood pressure, heart rate, temperature respirations, and pulse oximetry). See Section 5.5.3.
- ECOG performance status
- Blood chemistries
- PT/INR and aPTT
- Platelets, ANC and hemoglobin
- Urinalysis
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)
- Concomitant medications
- Imprime PGG
- Pembrolizumab
- Correlative samples:
  - Pre-dose serum sample for analysis of soluble PD-L1 level and PD-L1 expression on circulating mononuclear cells.

- Phase Ib: Pre Imprime PGG infusion: Serum for anti-β-glucan antibodies (ABAs), Imprime
- Phase II: Pre and post Imprime PGG infusion: Serum for anti-β-glucan antibodies (ABAs), Imprime
- Serum for immune classifiers
- See Correlative Laboratory Manual (CLM) for specific instructions.

- Banking samples.
  - Whole blood
  - Unstained slides from archived tissue
  - Serum and plasma
  - See CLM for specific instructions.

7.2.2. **Phase Ib: Cycle 1 Days 8, 15**

- Vital signs. See Section 5.5.3.
- ECOG performance status
- Blood chemistries
- PT/INR and aPTT
- Platelets, ANC and hemoglobin
- Urinalysis
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)
- Concomitant medications
- Imprime PGG

7.2.3. **Phase II: Cycle 1 Days 8, 15:**

- Vital signs (blood pressure, heart rate, temperature respirations, and pulse oximetry). See Section 5.5.3.
- Imprime PGG

7.2.4. **Cycles 2-4 Day 1:**

- Physical exam, weight
- Vital signs. See Section 5.5.3.
- ECOG performance status
- Blood chemistries
- Thyroid function (TSH, T3, T4). T3, T4: free or total as per local standards.
- Platelets, ANC and hemoglobin
- Urinalysis
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)
- Concomitant medications
- Imprime PGG
- Pembrolizumab
- Correlative samples:
  - Prior to Cycle 2: unstained slides from archived tissue for analysis of concentrations and localization (peri- vs. intratumoral) of NK cells, neutrophils, CD8+ T cells and PD-L1 biomarkers.

- Cycle 2 and Cycle 3 pre-dose serum samples for analysis of soluble PD-L1 level and PD-L1 expression on circulating mononuclear cells.
- Phase II only: Pre and post Imprime PGG infusion Cycles 2, 3, 5, 6, 7: Serum for anti-β-glucan antibodies (ABAs)
- See CLM for specific instructions.

7.2.5. **Cycles 2-4 Days 8, 15:**

- Vital signs (blood pressure, heart rate, temperature respirations, and pulse oximetry). See Section 5.5.3.
- Imprime PGG.
  - **NOTE**: For Phase II: Imprime PGG will be given on Day 1 of each cycle after cycle 4.

7.2.6. **Cycles 5-16 Day 1:**

- Physical exam, weight
- Vital signs. See Section 5.5.3.
- ECOG performance status
- Blood chemistries
- Thyroid function (TSH, T3, T4). T3, T4: free or total as per local standards.
- Platelets, ANC and hemoglobin
- Urinalysis
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)
- Concomitant medications
- Imprime PGG
- Pembrolizumab
- **Phase II** Correlative samples:
  - Cycle 5, 6, 7: Pre and post Imprime PGG: serum for anti-β-glucan antibodies (ABAs)
  - See CLM for specific instructions.

7.2.7. **Phase Ib: Cycles 5-16 Days 8, 15:**

- Vital signs (blood pressure, heart rate, temperature respirations, and pulse oximetry). See Section 5.5.3.
- Imprime PGG

7.2.8. **Day 1 of Every 2/3 Cycles (±7 days):**

- CT chest, abdomen, pelvis every 2 cycles while on study, starting within one week before Cycle 3 Day 1. CT pelvis is only required if there are known pelvic mets. If the subject has achieved at least stable disease after 7 cycles, disease assessment may be performed every 3 cycles thereafter until disease progression.

## 7.3. Off Treatment

7.3.1. **Protocol therapy discontinuation:**

A subject will be discontinued from the protocol therapy under the following circumstances:

- The subject completes the maximum of 16 cycles of study drug.
- If there is evidence of disease progression

- If the treating physician thinks a change of therapy would be in the best interest of the subject
- If the subject requests to discontinue protocol therapy
- If the protocol therapy exhibits unacceptable toxicity
- If a female subject becomes pregnant
- If there is a ≥ 12-week delay between cycles due to a treatment related adverse event.
- Subjects can stop study participation at any time. However, if they decide to stop, subjects will continue to be followed for survival for 5 years after start of study treatment.

7.3.2. **Safety Follow-up Evaluations (±7 days):**

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of study drug or before the initiation of a new anti-cancer treatment, whichever comes first.

- Physical exam, weight
- Vital signs (blood pressure, heart rate, temperature)
- ECOG performance status
- Assess adverse events (AE), events of clinical interest (ECI) and immune-related adverse events (irAE)
- Concomitant medications
- Banking samples
  - Serum and plasma
  - See CLM for specific instructions.

7.3.3. **Long Term Follow-up Evaluations (±14 days):**

- Subjects will continue to be followed for survival every 3 months for the first year from the start of study treatment. Thereafter, subjects will be followed for survival every 6 months for years 2-5 from the start of study treatment.
- Disease assessment via CT scan will be performed every 6 months for subjects who did not progress during treatment.

# 8. CRITERIA FOR DISEASE EVALUATION

Response assessments will be made using RECIST v1.1. The same measurable and non-measurable lesions will be followed by RECIST v1.1. Disease progression will be determined using RECIST v1.1 criteria.

## 8.1. Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1

8.1.1. **Measurable disease**

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

**8.1.1.1. Measurable lesions:**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

**8.1.1.2. Non-measurable lesions:**

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

**8.1.1.3. Malignant lymph nodes.**

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

**8.1.1.4. Baseline documentation of "Target" and "Non-Target" lesions:**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline.

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

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

## 8.2. Response Criteria for Target Lesions

### 8.2.1. Evaluation of Target Lesions:

**Table 5: Target Lesions Evaluation Response Criteria**

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

### 8.2.2. Evaluation of Non-Target Lesions:

**Table 6: Non-Target Lesion Evaluation Response Criteria**

| **Response Criteria** | **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) or/and 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* |
| * Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances. | |

## 8.3. 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 PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

**Table 7: Best Response Evaluation:**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/ Non-PD | No | PR |
| | Not evaluated | No | PR |
| PR | Non-CR/ Non-PD/ not evaluated | No | PR |
| SD | Non-CR/ Non-PD/ not evaluated | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD* | Yes or No | PD |
| Any | Any | Yes | PD |
| *In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. | | | |

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

## 8.4. Definitions for Response Evaluation –RECIST version 1.1

8.4.1. **First Documentation of Response:**
The time between initiation of therapy and first documentation of PR or CR.

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

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

8.4.4. **Duration of Overall Complete Response:**
The period measured from the time that measurement criteria are met for complete response until the first date that progressive disease is objectively documented.

8.4.5. **Response rate:**
The response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.

8.4.6. **Clinical Benefit Rate:**
The proportion of subjects with a confirmed complete response, a partial response or stable disease based on RECIST v1.1.

8.4.7. **Progression-Free Survival:**
A measurement from the start of the treatment until the criteria for disease progression is met as defined by RECIST v1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation. Subjects that receive at least one dose of study treatment and complete 1 post-baseline disease assessment or die prior to the first post baseline disease assessment will be considered evaluable for PFS.

8.4.8. **Overall Survival**
A measurement from the start of the treatment until death from any cause. Subjects alive at last time of contact will be right-censored.

# 9. BIOLOGICAL CORRELATIVES

**9.1. Correlate biomarkers on immune cell subset concentrations and localization in archived diagnostic tumor tissue with PFS and CBR (HiberCell).**
Biomarkers on immune cell subsets (including monocytes, macrophages, granulocytes, and lymphocytes) will be evaluated by multiplex immunofluorescence staining using the tyramide signal amplification (TSA) method (PerkinElmer) at HiberCell laboratories. This method allows for simultaneous detection of multiple (up to 8 different) markers in the same slide. Marker concentrations and localization (peri- vs. intratumoral) will be evaluated for each marker and then correlated with clinical response to therapy. Unstained slides will be provided for this analysis.

Refer to the CLM for collection, labeling and shipping instructions.

**9.2. Evaluate PD-L1 from diagnostic tissue (Dako)**
Expression of PD-L1 in archived diagnostic tumor tissue will be determined by referring laboratory (Dako) used by Merck. Unstained slides are to be submitted; a tumor block is not acceptable.
A fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen are not be acceptable for PD-L1 analysis. Refer to the CLM for collection, processing, labeling and shipping instructions.

**9.3. Correlate change in soluble PD-L1 level in serum with PFS and CBR (UIC).**
Whole blood for serum submission will be collected at pre-dose Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 for analysis of soluble PD-L1 levels. Change in soluble PD-L1 levels as a result of treatment will be examined in relation to PFS and CBR. This analysis will be determined by ELISA assay will be conducted at the University of Illinois Cancer Center. Refer to the CLM for collection, processing, labeling and shipping instructions.

**9.4. Correlate PD-L1 expression on circulating PBMCs from whole blood (HiberCell)**
Peripheral blood mononuclear cells will be collected at baseline (pre-dose Day 1 of Cycle 1) and on Cycle 2 Day 1 and Cycle 3 Day 1 for analysis of PD-L1 expression on circulating mononuclear cells. This analysis will be done in HiberCell laboratories. Refer to the CLM for collection, processing, labeling and shipping instructions.

**9.5. Correlate ABA levels (IgM, IgG) and FcγRIIa polymorphism with PFS and CBR (HiberCell).**
Phase Ib: Whole blood for serum will be collected at baseline (i.e., pre-dose Day 1 of Cycle 1) for analysis of anti-beta glucan antibody (ABA) (IgM, IgG) levels. Baseline ABA levels will be examined in relation to PFS and CBR.

Phase II: Whole blood for serum will be collected at pre and post Imprime PGG infusion at Cycles 1, 2, 3, 5, 6, and 7 for analysis of anti-beta glucan antibody (ABA) (IgM, IgG) levels. ABA levels will be examined in relation to PFS and CBR.

Both phases: Baseline (i.e., pre-dose Cycle 1 Day 1) FcγRIIa polymorphism will be examined in relation to PFS and CBR. Samples will be analyzed at HiberCell.

Refer to the CLM for collection, processing, labeling and shipping instructions.

**9.6. Correlate baseline proteomic immune classifiers with PFS and CBR.**
Whole blood will be collected at baseline for analysis of immune classifiers. Baseline proteomic immune classifiers will be examined in relation to PFS and CBR. Refer to the CLM for collection, processing, labeling and shipping instructions.

**9.7. Banking of Leftover Biospecimens**
Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN), as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

**9.8. Banking Samples for Future Unspecified Research**
Subject consent will be obtained to collect additional samples collected for future unspecified Big Ten Cancer Research Consortium studies. HCRN will manage the banked samples. Samples will be banked indefinitely in the HCRN Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at End of Treatment.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at End of Treatment.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the CLM for all sample collection, processing, labeling, and shipping instructions.

**9.9. Confidentiality of Biospecimens**
Samples that are collected will be identified by the subject's study number assigned at the time of trial registration. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

# 10.DRUG INFORMATION

## 10.1. Drug name: Imprime PGG: (Beta 1,3/1,6 glucan):

**Supplied as:**
Imprime PGG Injection is formulated as a sterile solution at 1.0 mg/mL and is supplied in 20 mL or 50 mL vials containing 20 mg or 50 mg, respectively, of Imprime PGG (1.0 mg/mL).

**Availability:**
Imprime PGG for investigational purposes will be provided by HiberCell at no charge to subjects participating in this clinical trial. Imprime PGG must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

**Storage, Handling, and Accountability**
Imprime PGG vials will be provided to the investigative site. Vials will be stored at controlled room temperature, 20º to 25ºC upon arrival at the site (excursions permitted between 15º and 30ºC). Formal studies to assess the stability of drug product at the recommended storage conditions have demonstrated that Imprime PGG is stable for at least 48 months. A packing list will be included with the shipment of clinical study material. Upon receipt of study drug, the site will inspect the shipment for any damage, and compare contents against the packing list. The site will acknowledge receipt of the shipment, noting any discrepancies or damages. Imprime PGG vials should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous particulates. Discard vials containing precipitate and request a replacement shipment. Total storage time of Imprime PGG diluted in the IV bag, inclusive of administration, cannot exceed 8 hours at room temperature or 24 hours at 2º to 8ºC.

**Administration**
Imprime PGG should be reconstituted in an appropriate volume of 0.9% sodium chloride injection, USP or equivalent normal saline infusion bags for administration by IV infusion through a low protein binding 0.22-micrometer in-line filter. Preparation under a hood is not required, but is preferable. An infusion pump should be used to ensure accurate and consistent dosing. Imprime PGG is to be administered via IV infusion over a 2-4 period depending on the subject's weight (see table below). Subjects will receive Imprime PGG at a dose determined by their weight. The table below describes total infusion volumes, administration times, and rate of infusion for study doses of 2 and 4 mg/kg. Extended infusion times are acceptable and will not incur a deviation; the rate of infusion should not be increased. Premedication as outlined in Section 5.2.

| Subject Weight (kg) | Total Infusion Volume (mL) | Infusion Time (hours) | Rate of Infusion (mL/min) |
|---|---|---|---|
| **2mg/kg Imprime PGG** | | | |
| ≤75 | 500 | 2 | 4.2 |
| >75 to ≤150 | 750 | 3 | 4.2 |
| >150 | 1000 | 4 | 4.2 |
| **4 mg/kg Imprime PGG** | | | |
| ≤75 | 500 | 2 | 4.2 |
| >75 to ≤150 | 750 | 3 | 4.2 |
| >150 | 1000 | 4 | 4.2 |

The Imprime PGG infusion should be prepared as follows:

**Preparation instructions for 2 mg/kg Imprime PGG:**

1. Determine the 2 mg/kg Imprime PGG dose/dose volume needed.
   - **Example A** (For weight <75 kg): Subject weighs 70 kg, 70 x 2 mg/kg = a total Imprime PGG dose of 140 mg. At the Imprime PGG vial concentration of 1mg/mL = 140 mLs of Imprime PGG. Imprime is supplied in 50 mL vials = 3 50-mL vials needed and prepared as described further in Steps 2 – 6 below.
   - **Example B** (For weight >75 kg, up to ≤150 kg): Subject weighs 100 kg, 100 x 2 mg/kg = a total Imprime PGG dose of 200 mg. At the Imprime PGG vial concentration of 1mg/mL= 200 mLs of Imprime PGG. Imprime PGG is supplied in 50 mL vials = 4 50-mL vials needed and prepared as described further in Steps 2 – 6 below.
   - **Example C** (For weight >150 kg): Subject weighs 160 kg, 160 x 2 mg/kg = a total Imprime PGG dose of 320 mg. At the Imprime PGG vial concentration of 1mg/mL = 320 mLs of Imprime PGG. Imprime PGG is supplied in 50 mL vials = 7 50-mL vials needed and prepared as described further in Steps 2 – 6 below.

2. Determine the required infusion size bag of 0.9% NS from the table above based on the subject's weight. Withdraw a volume of the 0.9% NS equal to the calculated Imprime PGG dose volume (from Step 1) and discard the withdrawn NS solution.
   - **Example A** (For weight <75 kg): Since subject weighs 70 kg, a 500 mL 0.9% NS bag should be used. Withdraw and discard 140 mLs of NS from the 500 mL NS bag.
   - **Example B** (For weight >75 kg, up to ≤150 kg): Since subject weighs 100 kg, a 750 mL 0.9% NS bag should be used. Withdraw and discard 200 mLs of NS from the 750 mL NS bag.
   - **Example C** (For weight >150 kg): Since subject weighs 160 kg, a 1000 mL 0.9% NS bag should be used. Withdraw and discard 320 mLs of NS from the 1000 mL NS bag.

3. Withdraw the calculated Imprime PGG dose volume from the Imprime PGG vials (from Step 1).
   - **Example A** (For weight <75 kg): From a total of 3 50-mL vials of Imprime PGG, withdraw the required 140 mg (140 mLs) and inject the Imprime PGG into the NS bag and mix gently.
   - **Example B** (For weight >75 kg, up to ≤150 kg): From a total of 4 50-mL vials of Imprime PGG, withdraw the required 200 mg (200 mLs) and inject the Imprime PGG into the NS bag and mix gently.
   - **Example C** (For weight >150 kg): From a total of 7 50-mL vials of Imprime PGG, withdraw the required 320 mg (320 mLs) and inject the Imprime PGG into the NS bag and mix gently.

4. Label bag appropriately.

5. Attach a low protein binding 0.22-micrometer in-line filter to appropriate IV tubing, and using an infusion pump infuse at the rate determined by the total infusion volume/infusion time described:
   - **Example A** (For weight <75 kg): Since subject's weight was 70 kg, a 500 mL total fluid volume was calculated. The length of infusion will be 2 hours at a rate of 4.2 mL/min
   - **Example B** (For weight >75 kg, up to ≤150 kg): Since subject's weight was 100 kg, a 750 mL total fluid volume was calculated. The length of infusion will be 3 hours at a rate of 4.2 mL/min

- **Example C** (For weight >150 kg): Since subject's weight was 160 kg, a 1000 mL total fluid volume was calculated. The length of infusion will be 4 hours at a rate of 4.2 mL/min

6. When infusion is complete, flush tubing with additional NS to ensure complete dosing.

**Preparation instructions for 4 mg/kg Imprime PGG:**

1. Determine the 4 mg/kg Imprime PGG dose/dose volume needed
   - **Example A** (For weight <75 kg): Subject weighs 70 kg, 70 x 4 mg/kg = a total Imprime PGG dose of 280 mg. At the Imprime PGG vial concentration of 1mg/mL = 280 mLs of Imprime PGG. Imprime is supplied in 50 mL vials = 6 50-mL vials needed and prepared as described further in Steps 2 – 6 below.
   - **Example B** (For weight >75 kg, up to ≤150 kg): Subject weighs 100 kg, 100 x 4 mg/kg = a total Imprime PGG dose of 400 mg. At the Imprime PGG vial concentration of 1mg/mL= 400 mLs of Imprime PGG. Imprime PGG is supplied in 50 mL vials = 8 50-mL vials needed and prepared as described further in Steps 2 – 6 below.
   - **Example C** (For weight >150 kg): Subject weighs 160 kg, 160 x 4 mg/kg = a total Imprime PGG dose of 640 mg. At the Imprime PGG vial concentration of 1mg/mL = 640 mLs of Imprime PGG. Imprime PGG is supplied in 50 mL vials = 13 50-mL vials needed and prepared as described further in Steps 2 – 6 below.

2. Determine the required infusion size bag of 0.9% NS from the table above based on the subject's weight. Withdraw a volume of the 0.9% NS equal to the calculated Imprime PGG dose volume (from Step 1) and discard the withdrawn NS solution.
   - **Example A** (For weight <75 kg): Since subject weighs 70 kg, a 500 mL 0.9% NS bag should be used. Withdraw and discard 280 mLs of NS from the 500 mL NS bag.
   - **Example B** (For weight >75 kg, up to ≤150 kg): Since subject weighs 100 kg, a 750 mL 0.9% NS bag should be used. Withdraw and discard 400 mLs of NS from the 750 mL NS bag.
   - **Example C** (For weight >150 kg): Since subject weighs 160 kg, a 1000 mL 0.9% NS bag should be used. Withdraw and discard 640 mLs of NS from the 1000 mL NS bag.

3. Withdraw the calculated Imprime PGG dose volume from the Imprime PGG vials (from Step 1).
   - **Example A** (For weight <75 kg): From a total of 6 50-mL vials of Imprime PGG, withdraw the required 280 mg (280 mLs) and inject the Imprime PGG into the NS bag and mix gently.
   - **Example B** (For weight >75 kg, up to ≤150 kg): From a total of 8 50-mL vials of Imprime PGG, withdraw the required 400 mg (400 mLs) and inject the Imprime PGG into the NS bag and mix gently.
   - **Example C** (For weight >150 kg): From a total of 13 50-mL vials of Imprime PGG, withdraw the required 640 mg (640 mLs) and inject the Imprime PGG into the NS bag and mix gently.

4. Label bag appropriately.

5. Attach a low protein binding 0.22-micrometer in-line filter to appropriate IV tubing, and using an infusion pump infuse at the rate determined by the total infusion volume/infusion time described:
   - **Example A** (For weight <75 kg): Since subject's weight was 70 kg, a 500 mL total fluid volume was calculated. The length of infusion will be 2 hours at a rate of 4.2 mL/min.

- **Example b** (For weight >75 kg, up to ≤150 kg): Since subject's weight was 100 kg, a 750 mL total fluid volume was calculated. The length of infusion will be 3 hours at a rate of 4.2 mL/min.
- **Example C** (For weight >150 kg): Since subject's weight was 160 kg, a 1000 mL total fluid volume was calculated. The length of infusion will be 4 hours at a rate of 4.2 mL/min.

6. When infusion is complete, flush tubing with additional NS to ensure complete dosing.

**Risks**
Imprime PGG is an investigational product that may only be used under the terms defined in this protocol and associated IB.

To date, 84 of the 103 healthy subjects enrolled into the Imprime PGG studies have been administered at least one dose of Imprime PGG. Of these 84 subjects, 27 subjects were administered Imprime PGG alone and 57 subjects were administered Imprime PGG and concomitant G-CSF (10 mcg/kg/day for four consecutive days). More specifically, 51 of the 84 subjects received single doses of Imprime PGG up to 6 mg/kg and 33 of the 84 subjects received multiple doses of Imprime PGG (single doses administered on either 2 days, 4 consecutive days, or 7 consecutive days) in doses up to 4 mg/kg. With regard to the 19 subjects receiving only placebo, 10 of these subjects were concomitantly also administered G-CSF (10 mg/kg/day for four consecutive days). Imprime PGG administration has demonstrated no tendency to result in life-threatening AEs, SAEs, or AEs of severe intensity in healthy volunteers.

In a metastatic CRC subject population, to date, 50 subjects have been administered Imprime PGG in the completed CRC0713 and CRC0821 studies. Subjects in the completed studies have been dosed for up to 64 weeks in combination with a standard regimen of cetuximab and irinotecan, or cetuximab alone. In the ongoing CRC1031 study, 141 subjects have received the combination of Imprime PGG plus standard regimen of cetuximab.

In an NSCLC subject population, to date, 118 subjects have been administered Imprime PGG in the ongoing studies LCA0821 and LCA0822. Subjects have been dosed for up to 69 weeks in combination with a standard regimen of bevacizumab, carboplatin and paclitaxel, and up to 54 weeks in combination with a standard regimen of cetuximab, carboplatin and paclitaxel.

Subjects should be continuously monitored for AEs and/or any safety concerns.

**Warnings and Precautions**
The drug is considered to be generally safe and well-tolerated.

## 10.2. Drug Name: Pembrolizumab (MK-3475 [Anti-PD-1 Antibody MK-3475])

**Chemical name and properties**
Humanized X PD-1_mAb (H409A11) IgG4

**Availability**
Merck will supply pembrolizumab at no charge to subjects participating in this clinical trial.
The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

**Storage**
Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

**Dosage and Administration**
Please refer to the Pharmacy Manual for a comprehensive description of pembrolizumab preparation.

Merck will supply pembrolizumab directly to sites at no cost to subjects in this clinical trial.

The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted product and liquid product is intended for IV administration. The reconstituted drug product solution and liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 96 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

**Side Effects**
Please refer to the current version of the Investigator's Brochure for a complete list of adverse events.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies that include adrenal insufficiency (primary and secondary) and hypophysitis (including hypopituitarism), thyroid disorder (hypothyroidism, hyperthyroidism and thyroiditis), Type I diabetes mellitus, uveitis, myositis, Guillain-Barre Syndrome, pancreatitis, myocarditis, myasthenic syndrome/myasthenia gravis (including exacerbation), encephalitis, sarcoidosis, severe skin reactions

including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and "solid organ transplant rejection following pembrolizumab treatment in donor organ recipients" (risk applicable to post-marketing setting only, as such patients are currently excluded from Merck clinical trials with pembrolizumab).

Immune-mediated adverse reactions (ARs), including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-mediated ARs can occur after discontinuation of treatment. Immune-mediated ARs affecting more than one body system can occur simultaneously. In clinical studies, most immune-mediated ARs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids, and/or supportive care.

The risk profile for pembrolizumab also includes 2 important potential risks – i.e. increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors; and GVHD after pembrolizumab administration in patients with a history of allogeneic HSCT.

One new identified risk of myelitis has been added to the Warnings and Precautions section of the Merck company core data sheet for pembrolizumab based on routine pharmacovigilance. In addition, new ADRs of Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis were identified based primarily on postmarketing reports.

Further details around frequency, reporting, and management of immune-related adverse events (irAEs) can be found in the current version of the Investigator's Brochure. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

# 11. ADVERSE EVENTS

## 11.1. Definitions of Adverse Events:

### 11.1.1. Adverse Event (AE):

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

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

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

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

### 11.1.2. Serious Adverse Event (SAE):

An SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Pembrolizumab overdose. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. See section 11.3 for further details.

11.1.3. **Unexpected Adverse Event:**

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

11.1.4. **Relatedness**

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

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

**11.2. Adverse Event (AE) Reporting:**

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

**11.3. Definition and Reporting of a Pembrolizumab Overdose:**

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

- If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
- If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 1 working day to BTCRC Administrative Headquarters (AHQ). BTCRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

**11.4. Reporting of Pregnancy and Lactation:**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 1 working day to BTCRC AHQ on the Pregnancy Report Form (See Documents/Info tab in the EDC). BTCRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

**11.5. Definition and Reporting of Events of Clinical Interest (ECI):**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported to BTCRC AHQ within 1 working day of the event.
Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined above, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3 × the upper limit of normal, **and** an elevated total bilirubin lab value that is greater than or equal to 2 × the upper limit of normal, **and**, at the same time, an alkaline phosphatase lab value that is less than 2 × the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *NOTE: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 1 working day to BTCRC AHQ. BTCRC AHQ will report the event within 1 working day to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220).

## 11.6. Serious Adverse Events (SAEs)

### 11.6.1. Site Requirements for Reporting SAEs to BTCRC Administrative Headquarters:

- SAEs will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form and entered in the SAE tab in the EDC system **within 1 business day** of discovery of the event.
- SAEs will be reported whether or not they are related to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

Non-serious Events of Clinical Interest will be reported to BTCRC AHQ and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator to be related to either study drug, which is brought to the attention of the investigator at any time outside of the 90-

day time period specified in the previous paragraph, also must be reported immediately to BTCRC AHQ.

The site will submit the completed SAE Submission Form (see Documents/Info tab in the EDC) to BTCRC AHQ within 1 working day of discovery of the event. The form will be sent electronically to safety@hoosiercancer.org. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

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

Once the SAE has resolved, sites must submit an electronic follow up SAE Submission Form within a reasonable timeframe to BTCRC AHQ at safety@hoosiercancer.org.

11.6.2. **BTCRC AHQ Requirements for Reporting SAEs to Merck and HiberCell:**
BTCRC AHQ will submit all immediately reportable events (e.g. SAEs, ECIs, overdose, pregnancy, etc.) received from sites to Merck and HiberCell within one working day of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

BTCRC AHQ will submit all SAE reports and any other relevant safety information to:

Merck Global Safety (Attn: Worldwide Product Safety) at:
Facsimile number: +1-215-993-1220
E-mail: AER_mailbox@merck.com

**and** to APCER (HiberCell Safety Designee):
SAE hotline
Fax: 609.531.0154
E-mail: safety.biothera@apcerpharma.com

BTCRC AHQ will provide follow-up information to Merck and HiberCell as reasonably requested.

## 11.7. BTCRC AHQ Responsibilities for Reporting SAEs to FDA

BTCRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. BTCRC AHQ will cross-reference this submission to Merck and HiberCell's parent INDs at the time of submission. Additionally, BTCRC AHQ will submit a copy of these documents to Merck and HiberCell at the time of submission to FDA.

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

## 11.8. Sponsor-Investigator Responsibilities

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

### 11.9. IND Safety Reports Unrelated to This Trial

Merck and HiberCell will send IND safety reports from external studies that involve the study drugs to BTCRC AHQ (safety@hoosiercancer.org). BTCRC AHQ will forward the safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. BTCRC AHQ will forward these reports to participating sites every 2 weeks.

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

## 12.STATISTICAL CONSIDERATIONS

### 12.1. Study Design:

This is a single arm study. Phase Ib: The primary objective of the Phase Ib dose escalation cohort study is to establish the MTD of study drug Imprime PGG when used in combination with pembrolizumab for subjects with NSCLC after failure of first line platinum-based chemotherapy. A standard "3+3" design will be used to establish the MTD.

Phase II: The primary objective of the Phase II trial is to estimate Progression-Free Survival (PFS) using RECIST v1.1 in subjects with metastatic non-small cell lung cancer (NSCLC) treated with Imprime PGG in combination with pembrolizumab after progression on first-line systemic therapy (either platinum-based chemotherapy with or without immune checkpoint inhibitor or immune checkpoint inhibitor as first line therapy). Pembrolizumab will be given on Day 1 and maximum tolerated dose of Imprime PGG will be given on Days 1, 8 and 15 for Cycles 1-4, and on Day 1 only for Cycles 5-16 of each 21 day cycle. Treatment continues until 16 cycles have been completed, disease progression, unacceptable toxicity, subject refusal, or subject death either from progression of disease, the therapy itself, or from other causes. Subjects who voluntarily stop the study, have progressive disease, or unacceptable toxicities will be followed for a total of 5 years.

Correlative research analyses include examining the relationship between PFS and CBR to immune biomarker (NK cells, neutrophils, CD8+ T cells and PD-L1) concentrations as well as localization (peri- vs. intratumoral) in the archived diagnostic tumor tissue and tumor vascular density. Research analyses also include examining the relationship between changes in soluble PD-L1 level and PD-L1 expression on circulating mononuclear cells at baseline (i.e., pre-dose Day 1 of Cycle 1) and during therapy (assessed pre-dose Cycles 2 and 3) and PFS and to CBR. Additionally, immune classifiers, FcγRIIa polymorphism, and anti-β-glucan antibody (ABA) (IgM, IgG) levels at will be correlated with PFS and CBR.

### 12.2. Criteria for Stopping Study:

The Phase Ib portion of the study will be stopped if 2 or more DLTs occur at dose level 1.

The Phase II portion of the study will be stopped if any grade 5 toxicity occurs which is thought to be directly attributable to the combination of Imprime PGG and pembrolizumab.

### 12.3. Sample Size:

Phase Ib: A standard "3+3" design will be used with maximum number of subjects accrued to be 12.

Phase II: Study endpoint will be progression-free survival (PFS), as assessed by the RECIST v1.1 criteria. The null hypothesis is that median PFS of combination drug is 3.2 months (equal to single agent pembrolizumab among subjects with a proportion score of 1 to 49%); the alternative hypothesis is that the PFS is 6.3 months (equal to single agent pembrolizumab among subjects with a proportion score of ≥ 50%).

The hypothesized median PFS is 6.3 months. With a total sample size of 24 we will have 90% power to detect a difference of 3.1 months (i.e., 6.3 months versus 3.2 months) with a two-sided exponential MLE test, controlling for a type I error probability of 5%. The power analysis was conducted using power calculation for one arm survival design proposed by Lawless.[39]

Unevaluable subjects will be replaced.

## 12.4. Analysis of Primary Objectives/Aims

**Phase Ib Analysis of Primary Endpoint:**
The primary endpoint is determination of the MTD of Imprime PGG. The MTD will be defined as the highest explored dose of Imprime PGG combined with 200 mg of pembrolizumab at which ≤1 out of 6 subjects have experienced a DLT within the first cycle of therapy. That dose will be recommended for the Phase II study (i.e., will be declared the RP2D). At the discretion of the sponsor-investigator, a lower phase II dose may be recommended if other toxicity emerges during the Phase Ib study which does not meet DLT criteria but limits the dose that can be administered cumulatively.

**Phase II Analysis of Primary Endpoint:**
The primary endpoint is determination of the activity of the combination of pembrolizumab and Imprime PGG in second line systemic therapy for NSCLC as assessed by progression-free survival based on RECIST v1.1. Median PFS times will be computed with associated 95% confidence intervals. Kaplan-Meier curves will be plotted.

## 12.5. Analysis of Secondary Endpoints:

### 12.5.1. Phase Ib Analysis of Secondary Endpoints

Characterize adverse effects (AEs) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line platinum-based chemotherapy.
Proportion of subjects with each grade of adverse events as defined by CTCAE v4 will be computed along with 95% confidence intervals and reported in a tabular and descriptive manner.

Estimate clinical benefit rate (CBR) (complete response, partial response, or stable disease) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line platinum-based chemotherapy.
CBR will be assessed every 2/3 cycles +/- 1 week while on study treatment using the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1- Section 8). Response will be reported via waterfall plot. Response outcome will be reported in a tabular manner. The response rate and 95% confidence interval for the response rate will be computed.

Estimate Progression-Free Survival (PFS) and 6-month PFS using RECIST v1.1 in subjects with NSCLC who progressed after first-line platinum-based chemotherapy when treated with Imprime PGG in combination with pembrolizumab.
Median PFS times will be computed, and PFS rate at 6 months +/- 1 month will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

Estimate overall survival (OS) and 1-year OS in subjects with NSCLC who progressed after first-line platinum-based chemotherapy when treated with Imprime PGG in combination with pembrolizumab.
Median OS times will be computed, and OS rate at 1 year +/- 3 months from start of study treatment will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

12.5.2. **Phase II Analysis of Secondary Endpoints**

Characterize adverse effects (AEs) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed after first-line systemic therapy
Proportion of subjects with each grade of adverse events as defined by CTCAE v4 will be computed along with 95% confidence intervals, and reported in a tabular and descriptive manner.

Estimate clinical benefit rate (CBR) (complete response, partial response, or stable disease) of Imprime PGG in combination with pembrolizumab in subjects with NSCLC who progressed on first-line systemic therapy.
CBR will be assessed every 2/3 cycles +/- 1 week while on study treatment using the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1- Section 8). Response will be reported via waterfall plot.

Estimate Progression-Free Survival (PFS) and 6-month PFS using RECIST v1.1 in subjects with NSCLC when treated with Imprime PGG in combination with pembrolizumab who progressed after first-line systemic therapy.
Median PFS times will be computed, and PFS rate at 6 months +/- 1 month will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

Estimate overall survival (OS) and 1-year OS in subjects with NSCLC treated with Imprime PGG in combination with pembrolizumab as first-line systemic therapy who progressed after first-line systemic therapy.
Median OS times will be computed, and OS rate at 1 year +/- 2 months will be calculated with associated 95% confidence intervals. Kaplan-Meier curves will be plotted. Data will be analyzed using the PROC LIFETEST in SAS.

**12.6. Analysis of Phase II Correlative Endpoints:**

- Immune biomarker (NK cells, neutrophils, CD8+ T cells and PD-L1) concentrations and localization (peri- vs. intratumoral) in archived diagnostic tumor tissue will be correlated with PFS and CBR. Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).

- Change in soluble PD-L1 level and PD-L1 expression on circulating mononuclear cells in serum pre-dose Cycles 2 and 3 relative to baseline (i.e., pre-dose Day 1 of Cycle 1) will be examined in relation to PFS and CBR. Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Correlation of ABA levels (IgM, IgG) to PFS and CBR. Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).
- Correlation of immune classifiers at baseline (i.e., pre-dose Day 1 of Cycle 1) to PFS and CBR. Spearman correlation will be computed using PROC CORR in SAS (Cary, NC).

# 13. TRIAL MANAGEMENT

## 13.1. Data and Safety Monitoring Plan:

The study will be conducted in accordance with the University of Illinois Cancer Center's Data and Safety Monitoring Plan (DSMP). The University of Illinois Cancer Center Data Safety and Monitoring Committee (DSMC) will review and make recommendations on this trial. BTCRC AHQ will provide the University of Illinois Cancer Center DSMC with periodic data reports to comply with the UICC DSMC review requirements.

In addition, BTCRC AHQ oversight activities include:

- Review of all adverse events requiring expedited reporting as defined in the protocol.
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator.
- Submit data summary reports to the lead institution DSMC for review as per their DSMP.

## 13.2. University of Illinois Cancer Center Data Safety Monitoring Committee

BTCRC AHQ will provide the UICC DSMC with the following:

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

The University of Illinois Cancer Center DSMC will review study data ever quarter. Documentation of DSMC reviews will be provided to the sponsor-investigator and BTCRC AHQ. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with BTCRC AHQ to address the DSMC's concerns.

## 13.3. Data Quality Oversight Activities

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

There will be at least one visit within a year of the first subject accrual per site. Additional for-cause visits may occur as necessary. Source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by BTCRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Merck, HiberCell, or their designee as well as inspection by appropriate regulatory agencies.

### 13.4. Compliance with Trial Registration and Results Posting Requirements

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

## 14.DATA HANDLING AND RECORD KEEPING

### 14.1. Data Management

BTCRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform compliant with Good Clinical Practices and Federal Rules and Regulations. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). BTCRC AHQ personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into the EDC system by study site personnel from participating institutions.

### 14.2. Case Report Forms and Submission:

An electronic case report form (eCRF) is required and must be completed for each included subject. The completed dataset is housed at BTCRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and BTCRC AHQ. After the initial publication, the complete data set will be available to all BTCRC institutions.

### 14.3. Record Retention:

To enable evaluations and/or audits from Health Authorities/BTCRC AHQ, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

### 14.4. Confidentiality

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

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number.

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

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

## 15.ETHICS

### 15.1. Institutional Review Board (IRB) Approval

The final study protocol, including the final version of the informed consent form, must be approved in writing by an IRB. The investigator must submit written approval by the IRB to the BTCRC AHQ office before he or she can enroll any subject into the study.

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

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

### 15.2. Ethical Conduct of the Study:

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

### 15.3. Informed Consent Process

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

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

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