SPONSOR: Biothera Pharmaceuticals, Inc.

TITLE: A Multicenter, Open-label, Phase 2 Study of Imprime PGG and Pembrolizumab in Subjects With Advanced Melanoma Failing Front-line Treatment with Checkpoint Inhibitors (CPI) or Triple Negative Breast Cancer (TNBC) Failing Front-line Chemotherapy for Metastatic Disease

Clinical Protocol BT-CL-PGG-MEL/BCA-1621 / MK3475 PN-545

Biothera

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1.0 TRIAL SUMMARY

Abbreviated Title	A Multicenter, Open-label, Phase 2 Study of Imprime PGG and Pembrolizumab in Subjects With Advanced Melanoma Failing Front-line Treatment with Checkpoint Inhibitors (CPI) or Triple Negative Breast Cancer (TNBC) Failing Front-line Chemotherapy for Metastatic Disease
Trial Phase	2
Clinical Indication	Advanced Melanoma and Triple Negative Breast Cancer
Trial Type	Multicenter, Simon's 2-stage optimal design of Imprime PGG and pembrolizumab
Type of control	Historical control
Route of administration	Intravenous for both products
Trial Blinding	None
Treatment Groups	All subjects to receive Imprime PGG + pembrolizumab
Number of trial subjects	Up to N=94 in total (up to 41 with advanced melanoma, up to 53 with TNBC)
Estimated duration of trial	Approximately 3 years
Duration of Participation	Approximately 2 years for any individual subject

2.0 TRIAL DESIGN

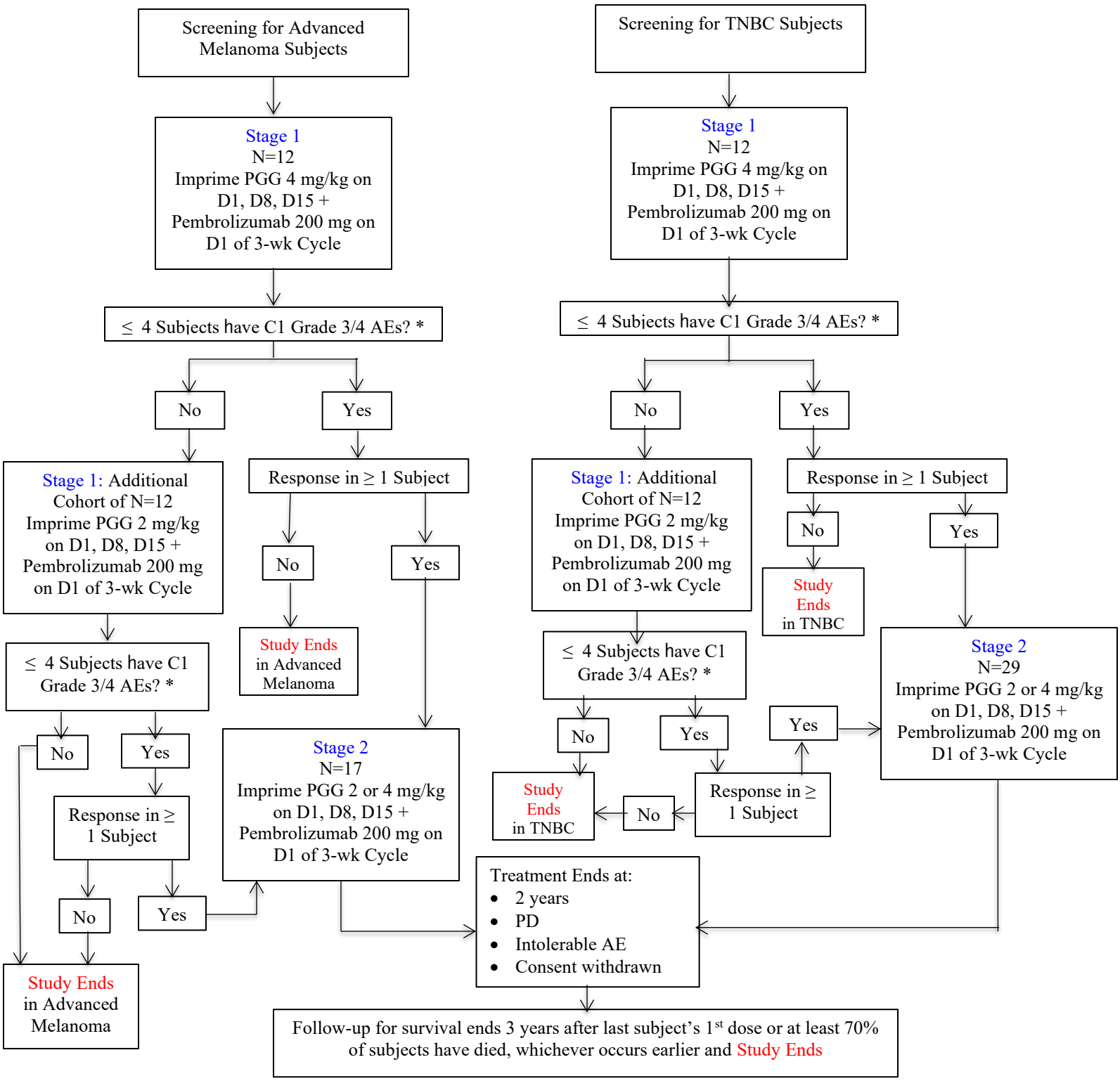
2.1 Trial Design

The study will incorporate Simon's optimal 2-stage design with sample size fixed at 12 subjects each in Stage 1 for advanced melanoma and for Triple Negative Breast Cancer (TNBC) subjects. The safety criterion of ≤ 4 (or $\leq 33\%$) subjects with Grade 3/4 adverse events in Cycle 1 within either tumor type must be met in order to proceed to Stage 2. The starting dose is 4 mg/kg for Imprime PGG. In the event there are a total of > 4 (or $> 33\%$) of subjects with Grade 3/4 adverse events in Cycle 1, the dose of Imprime PGG will be reduced to 2 mg/kg, and Stage 1 will be repeated at a dose of 2 mg/kg with an additional cohort of n=12 subjects. For the dose that meets the safety criterion in Stage 1, at least 1 response in melanoma subjects and 1 response in TNBC subjects amongst the 12 subjects within each tumor type must be observed in order to proceed to Stage 2.

Stage 2 will enroll an additional 17 subjects with melanoma, and 29 subjects with TNBC. For the dose that meets the Stage 1 safety criterion, success will be declared if at least 4 amongst the total of up to 29 subjects with melanoma, and 5 amongst the total of up to 41 subjects with TNBC achieve an objective response.

The study population will be those having failed front-line therapy, defined as any treatment regimen or regimens used specifically in the treatment of metastatic disease. Refer to Section 5.1 on Entry Criteria for the study-specific requirements.

2.2 Trial Diagram



* ≤ 4 subjects or 33% of Stage 1 subjects does not include infusion reactions (from either study drug) which were subsequently controlled and reduced in Cycle 1 via ameliorating actions, and which did not recur in Cycle 2

3.0 OBJECTIVES AND HYPOTHESIS

RECIST v1.1 criteria will be used for all applicable primary and secondary endpoints.

Immune related response criteria (irRECIST) will be used for exploratory efficacy endpoints.

3.1 Primary Objectives and Hypothesis

- **Objective:** To determine the Overall Response Rate (ORR) to Imprime PGG + pembrolizumab in subjects with advanced melanoma or metastatic TNBC
- **Safety:** To characterize the safety of Imprime PGG + pembrolizumab given in combination

Hypothesis: Restore (for melanoma) or enhance (for TNBC) sensitivity to checkpoint inhibitors (CPI) by appropriate and effective stimulation of the subject's innate and adaptive immune systems in those subjects who have failed front-line therapy

Melanoma Subjects:

- H_0: ORR $\leq$ 5%
- H_A: ORR $\geq$ 23%

TNBC Subjects:

- H_0: ORR $\leq$ 5%
- H_A: ORR $\geq$ 21%

Rejection of the null hypothesis will require documenting at least 4 objective responses among the total of up to 29 subjects with melanoma (Stage 1 + Stage 2), and 5 objective responses among the total of up to 41 subjects with TNBC (Stage 1 + Stage 2).

3.2 Secondary Objectives

Objectives:

- To determine the time to response (TTR), complete response rate (CRR), and duration of overall response (DoR) in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab
- To measure the Progression-Free Survival (PFS) and PFS rate at 6 months and 1 year in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab
- To measure overall survival (OS) and OS rate at 1 year in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab

- To profile pharmacokinetic (PK) data in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab

3.3 Exploratory Objectives

Objectives:

- Determine ORR and PFS based on irRECIST in subjects with advanced melanoma or metastatic TNBC when treated with Imprime PGG in combination with pembrolizumab
- Correlate levels of baseline serum anti-β-glucan antibody (ABA) with objective response and treatment outcomes
- Correlate changes in immune cell activation markers, such as CD86 expression in tumor biopsy samples* and in peripheral blood immune cells with objective response and treatment outcome
- In tumor biopsies, correlate changes in the tumor immune microenvironment including TILs (Tumor-infiltrating Lymphocytes) and tumor-infiltrating myeloid cells with objective response and treatment outcome
- Correlate PD-L1 expression in tumor biopsy samples (in tumor cells and myeloid cells) with objective response and treatment outcome

*Information on 1 tumor biopsy sample is required and is as follows: (1) Historical (diagnostic) tumor biopsy official pathology report +/- archival biopsy sample. Additional biopsy samples, preferably obtained from the same localized region, are highly desirable when feasible at the following time points: (2) Before the first dose of study treatment, (3) After completion of Cycle 2 but before the start of Cycle 3 dosing, and (4) At the time of response or disease progression, or at the End of Study Visit (if no response)

4.0 BACKGROUND AND RATIONALE

4.1 Imprime PGG Background

4.1.1 Imprime PGG – Therapeutic Mechanism of Action

Imprime PGG is a soluble, β-1,3/1,6 glucan isolated from the cell wall of a proprietary *Saccharomyces cerevisiae* yeast strain. Imprime PGG acts as a ***P***athogen-***A***ssociated ***M***olecular ***P***attern (PAMP). PAMPs are critical, "non-self" signals efficiently and effectively recognized by the different lineages of the innate immune system- macrophages, monocytes, neutrophils and dendritic cells. As a PAMP, Imprime PGG enhances innate immune cell killing, counteracts immune suppression and, importantly, triggers the activation and maturation of antigen presenting cells (ie, macrophages and dendritic cells), enabling T cell expansion and activation.

Non-clinical *ex vivo* studies using whole blood from healthy human volunteers have demonstrated that Imprime PGG treatment stimulates neutrophils to specifically recognize and kill antibody-decorated cancer cells via a remarkable burst in the generation of reactive oxygen species. Imprime PGG treatment also promotes the degranulation and the killing activity of Natural Killer (NK) cells directed against human cancer cells. M2 macrophages differentiated and isolated from Imprime PGG treated monocytes in human whole blood re-polarize, reducing expression of M2-specific surface markers (eg, CD163) and increasing M1-state markers (eg, CD86, PD-L1). These repolarized M2 macrophages exhibit significantly enhanced capacity to recognize and phagocytose antibody-decorated human cancer cells. Furthermore, these Imprime PGG treated M2 macrophages actively stimulate the expansion of CD4 T cells and the production of the potent anti-tumor cytokine IFNγ. Monocyte-derived dendritic cells (MoDCs) from Imprime PGG treated whole blood show increased expression of activation and maturation markers (CD80, CD83, CD86, HLA-DR), indicating these cells have matured into fully professional antigen presenting cells. In allogeneic Mixed Lymphocyte Reactions, these Imprime PGG-treated MoDCs can now instruct substantial CD4 and CD8 T cell expansion and increased IFNγ production. Collectively, these *ex vivo* studies suggest that Imprime PGG treatment drives the direct killing activity of innate immune effectors, re-polarizes the function of normally immunosuppressive M2 macrophages, and significantly enhances T cell priming, eliciting CD4 and CD8 T cell expansion and IFNγ production (Fraser et al, AACR 2016; Fulton et al, AACR 2016; Leonardo et al, AACR 2016; Jonas et al, AACR 2016).

In multiple pre-clinical tumor models *in vivo*, Imprime PGG has been shown to enhance the efficacy of tumor-targeted antibodies (eg, cetuximab). This anti-tumor response absolutely requires GR1+ (myeloid) cells, complement, and CR3. Recent *in vivo* work in preclinical tumor models further highlights the capacity of Imprime PGG to enlist the full functionality of the innate immune system to drive an anti-tumor response. In xenografted human tumor models, IV administration of Imprime PGG in conjunction with anti-angiogenic monoclonal antibodies (bevacizumab and DC101- a murine anti-VEGFR2 antibody) enhances anti-tumor efficacy while re-polarizing the immune microenvironment – ie, enhancing M1 marker expression (iNOS, TNFα, CD86, PD-L1), decreasing M2 marker expression (Arg1, TGFβ, CD206) and promoting differentiation of Myeloid Derived Suppressor Cells (MDSCs) (Fraser et al, AACR 2016 A; Fraser et al, AACR 2016 B; Jonas et al, AACR 2016). In the B16 melanoma model, Imprime PGG synergizes with the tumor targeting anti-Trp1 antibody in immune-competent C57BL/6 mice to significantly reduce the number and size of lung metastases (Leonardo et al, AACR 2016). Finally, in immune-competent C57BL/6 mice, IV administered Imprime PGG triggers mobilization of neutrophils and monocytes into circulation and into secondary lymphoid organs. Imprime PGG also effectively binds dendritic cells, inducing increased surface expression of CD86 and MHC class II, suggesting enhanced antigen presentation capability. Consistent with these data, Imprime PGG treatment specifically and robustly enhanced expansion of adoptively transferred CD8 T cells (the Ova-specific OT-1 cells) when co-injected with the model peptide antigen, Ova (Fulton et al, AACR 2016).

These *ex vivo* and *in vivo* data demonstrate that Imprime PGG treatment prompts a shift from an immunosuppressive microenvironment typified by M2 macrophages, MDSCs and immature dendritic cells, to an immune microenvironment characterized by M1 macrophages, differentiated MDSCs, and mature, activated dendritic cells. These data therefore suggest that Imprime PGG may enhance antigen presentation and cross-talk with T cells, thereby promoting the anti-tumor efficacy of checkpoint inhibitor therapy (eg, αPD-1 or αPD-L1 antibodies). Indeed, in multiple preclinical tumor models in syngeneic, immunocompetent mice, Imprime PGG enhances the efficacy of both anti-PD-1 and anti-PD-L1 antibody therapy. For instance, in the MC-38 tumor model, 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 83% (14/17) in mice treated with 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, whereas tumors readily established in age-matched, tumor naïve mice. These data suggest that Imprime PGG can boost the efficacy of checkpoint inhibitor therapy and further enhance immunologic memory (Fraser et al., AACR 2016 A and B).

Collectively, these studies demonstrate that Imprime PGG acts as a PAMP to enlist the broad functionality of the innate immune system to enhance the anti-tumor efficacy of tumor-targeting, anti-angiogenic, and immune checkpoint inhibitor monoclonal antibodies. Imprime PGG activates anti-cancer innate immune effector functions by triggering direct tumor killing by innate effector cells, overriding tumor-induced immunosuppression, and generating cross-talk with the adaptive immune system via enhanced activation of the antigen presenting cells.

In human serum, Imprime PGG forms an immune complex with anti-beta glucan antibodies (ABA), which activate the classical complement pathway, opsonizing the complex with complement. The opsonized Imprime PGG-ABA complex binds to FcγRIIa and complement receptor 3 (CR3), leading to subsequent modulation of innate immune effector cell functions (eg, IL-8 production) (Bose et al, Aug 2013; Qiu et al, 2014; Antonysamy et al, 2014; Keystone 2015). The formation of these immune complexes is necessary for Imprime PGG-induced innate effector cell function. Immune cells from human subjects with insufficient ABA do not respond to Imprime PGG unless supplemented with exogenous ABA. Responsiveness to Imprime PGG-based immunotherapy is predicated on ABA levels in individual subjects. Accordingly, pre-treatment ABA levels may represent a plausible, minimally invasive biomarker to enrich for patients most likely to benefit from Imprime PGG-based immunotherapy (Chan et al, 2016).

4.1.1.1 Imprime PGG in Healthy Volunteers

4.1.1.1.1 Completed Studies

Two Phase 1 studies in healthy subjects have evaluated single-dose, dose-escalations of Imprime PGG (doses of 0.5, 1, 2, 4 and 6 mg/kg; Study BIOBG-CL-001) and multiple-dose, dose-escalations of Imprime PGG (7 consecutive daily doses of 1, 2 and 4 mg/kg/day; Study BIOBG-CL-002).

Additionally, a Phase 1/2 study in healthy subjects evaluating co-administration of Imprime PGG (2 or 4 mg/kg) and granulocyte colony stimulating factor (G-CSF) for the mobilization of peripheral blood progenitor cells (PBPC) has been completed (Study BT-CL-PGG-SCM0611 [SCM0611]). Results of these studies are summarized in Section 5 of the Imprime PGG Investigators Brochure.

4.1.1.2 Imprime PGG in Cancer Patients

To date, Biothera has collected data from 5 cancer studies in which Imprime PGG has been administered in combination with anti-tumor monoclonal antibodies (mAbs). Three of these clinical studies have been completed with study reports, 1 has been completed and is awaiting a final study report, and 1 has completed the treatment phase and is in the process of closing.

4.1.1.2.1 Imprime PGG Completed Studies

- Study BT-CL-PGG-CRC0713 [CRC0713] evaluated administration of Imprime PGG in combination with cetuximab (Erbitux®), with and without standard irinotecan therapy, in subjects with metastatic colorectal cancer (mCRC). The primary objective of this study was to determine safety and maximum tolerated dose of Imprime PGG; key secondary objectives were to determine tumor response rates (including complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]), overall response rate (ORR), disease control rate (DCR), time to progression (TTP), and duration of tumor response; and to establish the pharmacokinetic (PK) profile in this setting. Subjects were enrolled into dose-escalating cohorts and dosed with either 2, 4, or 6 mg/kg Imprime PGG and a standard regimen of cetuximab either with concomitant irinotecan (Arm 1; 10 subjects) or without concomitant irinotecan (Arm 2; 22 subjects). Under a separate protocol, BT-CL-PGG-CRC0814 (CRC0814), tumor tissue samples from consenting subjects in this study were collected for *KRAS* gene status analysis. Complete safety and efficacy results of this study are summarized in Section 5 of the Imprime PGG Investigators Brochure. The results from the CRC0713 study (and associated CRC0814 protocol) formed the basis for the design of a Phase 3 study in *KRAS* wild type (WT) mCRC subjects that has completed the treatment phase (CRC1031 also known as PRIMUS).

- Study BT-CL-PGG-CRC0821 [CRC0821] assessed 4 mg/kg Imprime PGG with a standard regimen of cetuximab in the treatment of subjects with Stage IV, *KRAS*-mutated mCRC. The primary endpoint was ORR and key secondary endpoints included DCR, duration of response (DoR), TTP, PFS and OS. This study enrolled 18 subjects who had failed previous oxaliplatin and irinotecan-containing therapies. Results from the 18 subjects enrolled in Stage 1 show that 1 (5.6%) subject had a PR, and SD was observed in 9 (50.0%) additional subjects (of these 9 subjects SD was confirmed in 3 and unconfirmed in 6 subjects), yielding a DCR of 55.6% (10 total subjects with a response of SD or better). The DoR was 4.2 months for the subject with a PR, while the median duration of SD for the total 9 subjects with SD was 2.8 months (range: 0.4 – 7.2 months). In total, 13 (72.2%) subjects had documented

tumor progression. The median TTP was 2.7 months (range: 1.2-16.2 months). In total, 18 (100.0%) subjects had recurrence, progression, or death. The median PFS was 2.2 months (range: 1.2-16.2 months). In total, 16 (88.9%) subjects died. The median OS was 6.6 months (range: 1.9-23.1 months). These data compare favorably with historical responses of cetuximab monotherapy in KRAS mutated subjects where ORR, DCR, and median OS have been reported to be 0%-1%, 10%-30%, and 19-21 weeks, respectively. Complete safety and efficacy results are reported in Section 5 of the Imprime PGG Investigators Brochure.

- Study BT-CL-PGG-LCA0822 [LCA0822] assessed 4 mg/kg Imprime PGG in combination with cetuximab and a standard regimen of carboplatin and paclitaxel therapy in first-line treatment of late stage (Stage IIIB or IV) NSCLC. The primary endpoint was ORR; secondary endpoints included DCR, OS, tumor response rates (CR, PR, and SD), DoR, TTP, safety of regimen, and PK profile. A total of 90 subjects were enrolled. Of these, 59/60 subjects randomized into the Imprime PGG arm received this treatment (1/60 received no study treatment). Thirty (30) subjects were randomized into the control arm and of these, 29/30 received treatment (1/30 received no study treatment). This study was closed on 04 November 2015 with final results available in November 2015. The addition of Imprime PGG (4mg/kg intravenous infusion) to weekly infusions of cetuximab in combination with carboplatin and paclitaxel chemotherapy administered Q3W in subjects with advanced NSCLC resulted in improved ORR, the primary endpoint of the study (36.6% in the Imprime PGG arm vs. 23.1% in the Control arm [p=0.2895] based on central and 47.8% vs. 23.1% [p=0.0468], respectively, based on investigator assessment). Of the secondary endpoints, results were (Imprime PGG vs. Control): median DoR of 4.4 vs. 4.1 months by central review and 3.8 vs. 4.7 months by investigator assessment; median TTP of 6.4 months vs. 6.0 months (p=0.6044) by central review and 4.3 vs. 4.4 months (p=0.7305) by investigator assessment; median OS of 11.7 months vs. 12.4 months (p= 0.8972). All available efficacy and safety results are reported in Section 5 of the Imprime PGG Investigators Brochure.

- Study BT-CL-PGG-LCA0821 [LCA0821] assessed 4 mg/kg Imprime PGG in combination with a standard regimen of bevacizumab (Avastin®) and concomitant carboplatin and paclitaxel therapy in first-line treatment of late stage (Stage IIIB or IV) non-small cell lung cancer (NSCLC). The primary endpoint was ORR; secondary endpoints included DCR, OS, tumor response rates (CR, PR, and SD), DoR, TTP, PFS, TTR, safety of regimen, and PK profile. Ninety-two (92) subjects were randomized into the study. Of these, 59/61 randomized to the Imprime PGG arm received this treatment (2/61 received no study treatment). Thirty-one (31) were randomized to the control arm and of these, 30/31 received treatment (1/31 received no study treatment). This study was closed on 05 April 2016 with final results available in May 2016. Imprime PGG in combination with bevacizumab, carboplatin, and paclitaxel resulted in (Imprime PGG vs. Control): ORR of 60.4% vs. 43.5% (p=0.2096) based on independent central radiology review; median DoR of 10.3 vs. 5.6 mo (p=0.9040); median TTP of 11.6 mo vs. 9.6 mo (p=0.5639); median OS of

16.1 mo vs. 11.6 mo (HR 0.66; p=0.1345). All available efficacy and safety results to date are summarized in Section 5 of the Imprime PGG Investigators Brochure.

4.1.1.2.2 Study in Process of Closing (Treatment Phase Complete)

- Study BT-CL-PGG-CRC1031 [CRC1031 also known as PRIMUS] is a randomized, international, multi-center, Phase 3 study evaluating the efficacy and safety of the combination of Imprime PGG and cetuximab versus cetuximab alone in subjects with recurrent or progressive *KRAS* WT mCRC. Enrollment of up to 795 subjects was planned for this study, with up to 530 subjects randomized to the Imprime PGG arm, and up to 265 subjects randomized to the cetuximab-only control arm. The primary endpoint for this study is OS and key secondary endpoints include PFS, rates of response (CR, PR, and ORR), safety, PK profile, and changes in quality of life. Due to changes in standard of care since initiation of the study, continuing enrollment has proven to be not feasible, and further enrollment was halted on 23 September 2015. Subjects enrolled or randomized as of 23 September 2015 completed screening, treatment, and/or survival monitoring per protocol. In total, 140 subjects have received Imprime PGG 4 mg/kg with the standard cetuximab regimen, and 77 subjects have received the standard cetuximab without Imprime PGG regimen. While analysis of the data is ongoing, learnings from the biomarker assays have contributed to Biothera's understanding of biomarkers (see Section 4.3.3.2 Biomarker Research).

- Analysis of a Phase 1 study in healthy volunteers is currently ongoing. A total of 36 subjects in 3 cohorts were treated with Imprime PGG at doses of 4 mg/kg and 2 mg/kg. This study explored the immunopharmacodynamic characteristics of Imprime PGG through assessment of the following parameters: activation of blood leukocytes, concentrations of ABA, circulating opsonized immune complexes, concentrations of cytokines, total complement levels (CH50), polymorphism of FcγRII sequence, effect of prophylactic antihistamine/corticosteroid premedication on PD effects, and PK of serum Imprime PGG. In addition, kinetics of decay and recovery of pharmacodynamic responsiveness following Imprime PGG may be assessed, as well as the safety of Imprime PGG in symptomatology of adverse events, physical examination (if indicated), serum chemistry, changes in differential blood cell counts, blood coagulation parameters, urinalysis, and ECG.

4.2 Pembrolizumab Background

Refer to the pembrolizumab (KEYTRUDA®) Investigators Brochure/approved labeling for detailed background information on pembrolizumab.

4.2.1 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in

various malignancies (Mei 2014, Salgado 2014, Schatton 2014, Gooden 2011, Schreiber 2011, Bremnes 2011, Talmadge 2011, Shirabe 2010, Nosho 2010, Bellati 2009, Oble 2009, Uppalari 2008, Dunn 2007). In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors (Nosho 2010, Chang 2014, Preston 2013, Yoon 2012, Kim 2013, Mathai 2012, Liu 2011, Kirk 2010).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem 2014). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone (Zhang 2004) and in complex with its ligands were first resolved (Lazar-Molnar 2208, Lin 2008), and more recently the NMR-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported (Cheng 2013). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM), and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3zeta, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade (Sheppard 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 (Ott 2013). PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs and Natural Killer cells (Yao 2014). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells (Nishimura 1996), as well as subsets of macrophages (Huang 2009) and dendritic cells (Pena-Cruz 2010). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (Keir 2008). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (Karim 2009). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (Karim 2009, Taube 2012), which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (Sammamed 2014). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (Topalian 2012).

4.2.2 Pembrolizumab Background and Clinical Trials

Pembrolizumab [KEYTRUDA® (US)], a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the US and EU it is approved for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of patients with NSCLC in several countries; the US and the European Commission have indicated it for either first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, or for those 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. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. In the United States, pembrolizumab was granted accelerated approval for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy, and for patients locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. Pembrolizumb has also been approved for the treatment of Classical Hodgkin Lymphoma, for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, and for colorectal cancer patients with a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) biomarker following progression on a fluoropyrimidine, oxaliplatin, and irinotecan. Pembrolizumab is administered once every 3 weeks (Q3W), and can be administered for up to 35 cycles.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Keytruda® (Pembrolizumab) Investigators Brochure.

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Subject Population

With the approval and use of pembrolizumab in 1st line therapy for advanced melanoma, the options to continue deriving benefit from CPI treatment in 2nd line or further have been considerably limited if not eliminated altogether for patients with advanced melanoma. It is therefore of interest to explore whether sensitivity to CPI can be restored in 2nd line or further treatment by appropriate and effective stimulation of the patient's innate and adaptive immune system.

Pembrolizumab has also demonstrated clinical activity in subjects with metastatic TNBC. Study KEYNOTE-012 enrolled subjects with a variety of solid tumors, including a cohort of 32 subjects with metastatic or recurrent TNBC, an ECOG performance status of 0 or 1, and positive for PD-L1 expression. The median age was 50.5 years and most were heavily pretreated, in both the early and advanced settings (47% of subjects having received at least 3 lines of therapy for metastatic disease and 25% at least 5). In the 27 subjects who were evaluable for response, ORR was 18.5%, including 1 CR. Stable disease and progressive disease were reported in approximately 26% and 48% of subjects, respectively. The median time to response (TTR) was 18 weeks, and the median PFS was 1.9 months. The median duration of SD was 17 weeks, while median OS was 11.2 months (Nanda et al., 2016).

Study KEYNOTE-086 Cohort A enrolled a total of 170 subjects with centrally confirmed metastatic TNBC, ≥ 1 prior chemotherapy for metastatic disease, ECOG performance status of 0 or 1, and had pembrolizumab 200 mg every 3 weeks for up to 24 months. The median age was 54 years and 44% of subjects received at least 3 lines of therapy for metastatic disease. The ORR was 5% regardless of PD-L1 expression. Best overall response was 0.6% CR, 4% PR, and 21% SD. Median DOR was 6.3 months (range 1.2+ to 10.3+). Median PFS and OS were 2.0 moths (95% CI 1.9-2.0) and 8.9 months (95% CI 7.2-11.2) respectively (Adams et al., 2017).

Though in KEYNOTE-012, 18.5% of the subjects with PD-L1+ TNBC experienced an objective response, further data from the Phase 2 KEYNOTE-086 study showed the ORR was approximately 5% regardless of PD-L1 expression. These data highlight the need for further improvements in pembrolizumab-based combination immunotherapy.

Preclinical studies have now shown that Imprime PGG significantly enhances the anti-tumor efficacy of checkpoint inhibitor therapy in multiple, syngeneic (immune-competent) tumor models. This synergy likely reflects the mechanism of action for Imprime PGG - specifically, Imprime PGG-induced immune microenvironmental activation as well as the activation and maturation of professional antigen-presenting cells (dendritic cells). This synergy, and the mechanistic complementarity of pembrolizumab and Imprime PGG, provide compelling rationale for testing this combination clinically.

Importantly, recent research has now revealed that Imprime PGG forms an immune complex with naturally occurring anti-β-glucan antibodies (ABA) and that this complex is necessary for Imprime induced immune activation and anti-tumor immune effects (Chan et al, 2016). Furthermore, evidence from Imprime PGG clinical trials suggests that IgG pretreatment ABA levels in peripheral blood may act as a predictive biomarker of clinical activity of Imprime PGG (company data on file). In line with this evidence, subjects enrolled in this study will be required to have pre-specified ABA levels in peripheral blood.

In this study, subjects with advanced melanoma or TNBC failing front line treatment with CPI (melanoma) or chemotherapy (TNBC), will receive combination therapy with pembrolizumab and Imprime PGG with the purpose of assessing whether a further response (melanoma) or an increased response (TNBC) can be obtained by adding Imprime PGG to pembrolizumab. An ORR of 23% in melanoma subjects and of 21% in TNBC subjects would be considered clinically significant and relevant findings in these patient populations.

4.3.2 Rationale for Dose Selection/Regimen/Modification

The dose of 4 mg/kg of Imprime PGG administered IV over 2 hours is based on the results of the normal volunteer and oncology clinical studies in over 400 human subjects, including over 300 cancer subjects in combination with diverse monoclonal antibodies. A description of these studies and the study results is presented in Section 4.1.1.1 and Section 4.1.1.2. Additional details may be found in the Imprime PGG Investigators Brochure.

The dose of 2 mg/kg of Imprime PGG administered IV over 2 hours is based on the results of the normal volunteer and oncology clinical studies BIOBG-CL-001, BIOBG-CL-002, BT-CL-PGG-SCM0611, and BT-CL-PGG-CRC0713 in approximately 47 human subjects, including cancer subjects. A description of these studies and the study results is presented in the Imprime PGG Investigators Brochure.

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001 was an open-label Phase 1 study conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established

in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

4.3.3 Rationale for Endpoints

The primary and secondary endpoints selected will allow for assessment of whether a further response (melanoma) or an increased response (TNBC) can be obtained by adding Imprime PGG to pembrolizumab. An ORR of 23% in the melanoma subjects and of 21% in the TNBC subjects would be considered clinically significant and relevant findings in these patient populations.

This clinical study will also explore a number of translational research parameters and biomarkers germane to Imprime PGG and to the mechanisms of anti-tumor immunity. Specifically, evidence of myeloid cell activation at the tumor site, in peripheral blood (increase in CD86, PD-L1), in dendritic cell activation, and increased tumor lymphocyte infiltration (especially CD8+ T cells) in tumor biopsies will be measured. Their correlation with the observed clinical outcomes and their value at helping identify subgroups of interest will be assessed. It is expected that these cellular, immunological and biochemical parameters will inform on the factors at play in the response to therapy with pembrolizumab plus Imprime PGG, and help design and manage future studies of this combination.

4.3.3.1 Endpoints

Primary:

The primary efficacy endpoint is ORR, which is defined as the proportion of subjects demonstrating complete response (CR) or partial response (PR) based on RECIST v1.1 criteria.

Safety endpoints include the incidence of adverse events, serious adverse events, laboratory safety tests (eg, hematology, clinical chemistry), and ECOG performance.

Secondary:

Measurement of the secondary endpoints is based on RECIST v1.1 criteria.

- Time to response (TTR) is defined as time from first dose of study treatment (Study Day 1) to first response (CR or PR)
- Complete response rate (CRR) is defined as the proportion of subjects demonstrating CR
- Duration of response (DoR) is defined as the time from the first documented evidence of CR or PR until time of documented disease progression (PD) or death due to any cause, whichever is first
    - For responders who are lost to follow-up or who discontinue study before PD or death, DoR will be censored at the date of last radiological assessment
- Progression-free survival (PFS) is defined as:
    - Time from Study Day 1 until PD or death due to any cause, whichever occurs first
    - For subjects who are lost to follow-up or who discontinue study before PD or death, PFS will be censored at the date of the last radiological assessment
- Overall survival (OS) is defined as:
    - Time from date from Study Day 1 until date of death due to any cause
    - For subjects who have not died or who are lost to follow-up or withdrew consent, OS will be censored at the date of last contact
- Pharmacokinetic profile

Exploratory:

- ORR, as defined by irRECIST
- PFS, with date of PD as defined by irRECIST

The following exploratory analyses will be conducted to examine the relationship between biomarker data and endpoints if the data warrants:

- Analysis of ABA and endpoints
- Analysis of change in the immune cell activation markers and endpoints
- Analysis of change in the tumor immune microenvironment and endpoints

4.3.3.2 Biomarker Research

Mechanistically, Imprime acts as pathogen-associated molecular pattern (PAMP) directly activating innate immune effector cells and triggering a coordinated anti-cancer immune response. In *ex vivo* systems, using whole blood from healthy human subjects, Imprime-induced anti-cancer functionality is dependent on immune complex formation with naturally-occurring, anti-β glucan antibodies (ABA). The formation of Imprime:ABA complexes activates complement, primarily via the classical complement pathway, and is opsonized by iC3b. Immune complex binding depends upon Complement Receptor 3 and Fcγ Receptor IIa, eliciting phenotypic activation of, and enhanced chemokine production by, neutrophils and

monocytes, enabling these effector cells to kill antibody-opsonized tumor cells via the generation of reactive oxygen species and antibody-dependent cellular phagocytosis. Importantly, these innate immune cell changes are not evident in subjects with low ABA levels but could be rescued with exogenous ABA supplementation. Thus, pre-existing ABA are essential for Imprime-mediated anti-cancer immune activation (Chan et al, manuscript in preparation). These findings have also been corroborated in healthy subjects dosed *in vivo* with Imprime (ongoing findings from Study BT-CL-PGG-HHV1516).

Analysis from a Biothera-sponsored randomized clinical study in colorectal cancer subjects in N=168 subjects (CRC1031 also known as PRIMUS) established a correlation between IgG ABA level and increased PFS and OS only in subjects treated with Imprime PGG. Exploration of ABA IgG cutoffs indicate that hazard ratios (HRs) for both PFS and OS are more favorable when ABA IgG > 20 mcg/mL. A similar relationship of this ABA IgG cutoff to OS was observed in study BT-CL-PGG-LCA0822 [LCA0822] which assessed Imprime PGG in combination with cetuximab and a standard regimen of carboplatin and paclitaxel therapy in first-line treatment of late stage (Stage IIIB or IV) NSCLC. In this study, ABA IgG levels > 23.4 mcg/mL showed an increased OS (HR=0.58, CI 0.3-1.13, p=0.105). Finally, in studies of healthy human volunteers dosed with Imprime PGG, the biological activities associated with Imprime PGG (complement activation, white blood cell mobilization, and cytokine production) were never observed in volunteers that had ABA IgG levels < 20 mcg/mL, whereas most of these activities were evident in volunteers with ABA IgG levels > 20 mcg/mL.

Based on the above findings, only those subjects with serum IgG ABA levels ≥ 20 mcg/mL will be selected for treatment in this protocol. Analysis of ABA IgG levels in all cancer patients in trials where Imprime PGG has been dosed reveals an overall median ABA IgG level of 18.2 mcg/mL (ranging between median values of 14.3-23.0 mcg/mL depending on the trial). This indicates that at an ABA IgG value of 20 mcg/mL, the population will be approximately equally split by those above and below this value. Thus, for considerations of enrollment, it is expected that using an ABA IgG cutoff of 20 mcg/mL should include approximately 50% of subjects. Biothera has developed a technical-qualified manual, direct enzyme-linked immunosorbent assay (ELISA) to measure IgG ABA serum concentrations. The assay is in the process of being transferred to a College of American Pathologists (CAP)-accredited, Clinical Laboratory Improvement Amendment (CLIA)-environment laboratory.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Subjects with advanced melanoma or triple negative breast cancer failing front-line therapy for advanced disease.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have signed an informed document prior to any study-specific procedures or treatment
2. Be ≥ 18 years of age at time of consent
3. For Melanoma Subjects: Have histologically or cytologically confirmed diagnosis of unresectable Stage III or metastatic (Stage IV) melanoma not amenable to local therapy, and irrespective of PD-L1 status
4. For TNBC Subjects: Have histologically or cytologically confirmed diagnosis of metastatic (Stage IV) TNBC, and irrespective of PD-L1 status. TNBC is defined as negative immunohistochemistry (IHC) assays for Estrogen Receptor (ER), and Progesterone Receptor (PR), and HER2 negative (IHC 0 or 1+, or 2+ by IHC confirmed negative by FISH)
5. Have documented objective radiographic or clinical disease progression:
   a. For Melanoma: After PD-1/PD-L1 +/- anti-CTLA-4 inhibitor therapy
   b. For TNBC: After 1 or more prior lines of chemotherapy for metastatic disease
6. Have resolution of all previous treatment-related toxicities to Grade 1 severity or lower, except for stable sensory neuropathy (less than or equal to Grade 2) or alopecia. If subject received major surgery or radiation therapy of > 30 Gy, must have recovered from the toxicity and/or complications from the intervention.
7. Have at least one radiologically measurable lesion as per RECIST v1.1 defined as a lesion that is at least 10 mm in longest diameter or lymph node that is at least 15 mm in short axis imaged by CT scan or MRI and obtained by imaging within 28 days prior to start of study treatment. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Have peripheral blood levels of IgG anti-β-glucan antibody (ABA) of ≥ 20 mcg/mL as determined by an ELISA test prior (within 90 days) to start of study treatment
9. Be willing to consider providing fresh tissue for biomarker analysis, and, based on the adequacy of the tissue sample quality, for assessment of biomarker status. Repeat samples may be required if adequate tissue is not provided. Newly obtained biopsy specimens are preferred to archived samples and formalin-fixed, paraffin-embedded block specimens are preferred to slides.

   Note: Information on 1 tumor biopsy sample is mandatory and is as follows: (1) To determine eligibility, historical (diagnostic) tumor biopsy official pathology report +/- an archival sample. Additional biopsy samples, preferably obtained from the same localized region, are highly desirable when feasible at the following time points: (2) Sample before the first dose of study treatment, (3) Sample after completion of Cycle 2 but before the start of Cycle 3 dosing, and (4) Sample either at the time of response or at the End of Study Visit (if no response).

10. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 14.3)
11. Have life expectancy of 3 months or greater as determined by the treating physician
12. Have adequate organ function (all screening labs should be performed within 15 days prior to start of study treatment):
    a. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
    b. Aspartate aminotransferase (AST) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
    c. Alanine aminotransferase (ALT) ≤ 2.5 × ULN or ≤ 5 × ULN for subjects with known hepatic metastases
13. Have adequate renal function within 15 days prior to start of study treatment as defined by the following criteria:

    Creatinine ≤ 1.5 x ULN and CrCl ≥ 30 ml/min per Cockcroft Gault formula:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

14. Have adequate hematologic function within 15 days prior to start of study treatment, defined as meeting all of the following criteria:
    a. Hemoglobin ≥ 9 g/dL (uncorrected by RBC transfusion)
    b. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
    c. Platelet count ≥ 100 × 10^9/L
15. Have adequate coagulation functioning within 15 days prior to start of study treatment, defined by either of the following criteria:
    a. INR < 1.5 × ULN
    b. **OR** for subjects receiving warfarin or low molecular weight heparin (LMWH), 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 may exceed 1.5 × ULN if that is the goal of anticoagulant therapy.
    c. Activated Partial Thromboplastin Time (aPTT) < 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
16. Female subjects of childbearing potential as defined in Section 5.7.2 must have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
17. If of childbearing potential as defined in Section 5.7.2, must be willing to use an adequate

method of contraception (see Section 5.7.2) from the first dose of study medication through 120 days after the last dose of study medication

18. Be willing and have the ability to comply with scheduled visits (including geographical proximity), treatment plans, laboratory tests, and other study procedures

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has disease that is suitable for local therapy administered with curative intent
2. Is currently participating or has received an investigational agent or used an investigational device within 4 weeks of the first dose of treatment
3. Has a diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
4. Has known history of active tuberculosis
5. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)
6. Has known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected
7. Has a history of clinically severe autoimmune disease, or history of organ transplant
8. Has a history of ocular melanoma
9. Has known hypersensitivity to baker's yeast
10. Had previous exposure to Betafectin® or Imprime PGG
11. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients
12. Had a prior anti-cancer monoclonal antibody (except immune CPI in the case of melanoma subjects) within 30 days prior to start of study treatment, or failure to recover to CTCAE Grade 1 or better from the adverse events of prior therapies
13. Had within 2 weeks prior to Study Day 1, received prior chemotherapy, targeted small molecule therapy, or radiation therapy or who has not recovered from adverse events due to a previously administered agent or major surgery
14. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF, or recombinant erythropoietin) within 4 weeks prior to Study Day 1
15. Has known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

16. Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
17. Has active autoimmune disease requiring systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteriod replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
18. Has evidence of (non-infectious) pneumonitis that required steroids or current pneumonitis
19. Has a history of interstitial lung disease
20. Has an active infection requiring systemic therapy
21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator
22. Has a clinically significant cardiovascular disease such as unstable angina, myocardial infarction, or acute coronary syndrome within ≤180 days prior to start of study treatment, symptomatic or uncontrolled arrhythmia, congestive heart failure, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification
23. Has a known psychiatric or substance abuse disorder(s) that would interfere with informed consent or cooperation with the requirements of the trial
24. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment
25. Has received:
    a. For Melanoma: Has received any prior oncolytic vaccine
    b. For TNBC: Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-CTLA-4, or anti-PD-L2 agent
26. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

5.2 Trial Treatments

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

Please refer to Section 4.2.2.

If Stage 1 proceeds without the need for any dose modification as described in Section 5.2.1.2.1, Imprime PGG will be administered to all subjects at a dose of 4 mg/kg IV over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle. Refer to Appendix 14.1 for further details.

If enrollment into an additional cohort in Stage 1 is necessitated based on the dose modification requirements as described in Section 5.2.1.2.1, Imprime PGG will be administered to all subjects in the specified indication at a dose of 2 mg/kg IV over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle. Refer to Appendix 14.1 for further details.

Imprime PGG will always be administered first, followed 15-30 minutes later only on Day 1 of each cycle by pembrolizumab administration.

The pembrolizumab fixed dose of 200 mg will be administered IV over 30 minutes on Day 1 of each 3-week treatment.

5.2.1.2 Dose Modification

5.2.1.2.1 Imprime PGG

Each cycle will be 3 weeks in duration. The dose of Imprime PGG may be delayed or reduced as described below, due to the occurrence of infusion reactions or other adverse events.

Per CTCAE guidelines, mild-to-moderate reactions (Grades 1 and 2) are characterized by flushing, rash, fever, rigors, chills, dyspnea, nausea, back pain, and mild hypotension. Severe reactions (Grades 3 and 4) are associated with bronchospasm and hypotension requiring treatment, cardiac dysfunction, anaphylaxis, abdominal cramping, and other symptoms. The preferred order for actions the Investigator may take to ameliorate infusion reactions are listed below:

1. **Premedication(s)**
   Subjects may receive pre-treatment with standard anti-histamine medications before commencing dosing of study medications on each treatment day and, as needed, post-dose.

   Premedications:
   - Cycle 1/Day 1: Pretreat with an H1 antagonist (eg, 50 mg of diphenhydramine IV)

- Subsequent cycles: Premedication is allowed for each Imprime PGG infusion, but if tolerated by the subject and if medically appropriate, reduced premedication doses from those administered at Cycle 1/Day 1 should be used

2. **Infusion Time Extension**
   The infusion time should be lengthened from 2 hours to 4 hours and the infusion flow rate should be adjusted accordingly to 50% of the previous rate.

3. **Dose Reduction**
   If a subject experiences an infusion reaction despite having been administered premedication and despite the infusion time being lengthened, the PI may re-challenge the subject at the next visit by dose reducing the Imprime PGG to 2 mg/kg.

All attempts should be made to ameliorate Grade 3/4 infusion reactions by the Investigator following the 3 recommendations provided above sequentially.

In Stage 1, any Grade 3/4 infusion reactions mitigated by these actions and either resolving or decreasing to Grade 1/2, if this mitigation occurs within Cycle 1 and the Grade 3/4 infusion reaction does not recur in Cycle 2, will not be counted towards the total of > 4 or 33% of Grade 3/4 adverse events which require halting the study in Stage 1 for each individual indication. Only Cycle 1 Grade 3/4 infusion reactions (or those which recur in Cycle 2) will be counted towards the total which would halt advancement to Stage 2.

- In the event there are a total of > 4 or 33% of Grade 3/4 adverse events in Stage 1 which were unable to be ameliorated by the sequential recommendations above, the dose of Imprime PGG will be reduced to 2 mg/kg.

- Stage 1 will be repeated with an additional cohort of n=12 subjects at the reduced dose of 2 mg/kg. Toxicity at the dose of 2 mg/kg will be assessed in this additional Stage 1 cohort in the same manner as was done for the initial dose of 4 mg/kg, with the identical sequential recommendations for any observed infusion reactions.

- Advancement to Stage 2 will be halted if there are > 4 or 33% of Grade 3/4 adverse reactions. Otherwise, subjects will proceed to Stage 2 with all subjects at the new, reduced dose of 2 mg/kg.

Note that continuation onto Stage 2 requires a demonstration of at least 1 or 2 objective responses in subjects with melanoma or TNBC, respectively, in addition to meeting the adverse event requirements detailed above, at either Imprime PGG dose of 4 mg/kg or 2 mg/kg. Please refer to the Trial Diagram in Section 2.2 for a schema of the study flow from start to end.

In general, any Grade 4 non-infusion or non-hematological AE will lead to the withdrawal of the subject from treatment. A dosing delay of up to 3 weeks is allowed in case of Grade 3 non-hematological AEs to reduce toxicity to baseline or Grade 0-1. Dose levels will be adjusted individually for each study drug.

5.2.1.2.2 Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related adverse events (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial 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, or 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 as per Table 1 below.

Table 1. Dose Modifications 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 (CTCAEv4.03)	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 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • 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 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects 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). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects 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 1-2mg/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 subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects 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		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. 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		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician.
2. For subjects 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).

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. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reactions are provided in Table 2.

Table 2. Infusion Reaction Treatment Guidelines for Pembrolizumab

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 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 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, 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. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrines** IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) at http://ctep.cancer.gov		

In Stage 1, any Grade 3/4 infusion reactions mitigated by these actions and either resolving or decreasing to Grade 1/2, if this mitigation occurs within Cycle 1 and the Grade 3/4 infusion reaction does not recur in Cycle 2, will not be counted towards the total of > 4 or 33% of Grade 3/4 adverse events which require halting the study in Stage 1 for each individual indication. Only Cycle 1 Grade 3/4 infusion reactions not controlled by the above measures (or those which recur in Cycle 2) will be counted towards the total which would halt advancement to Stage 2.

Dose will be managed individually for each study drug.

5.2.1.3 Dose Interruptions

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

5.2.2 Timing of Dose Administration

If Stage 1 proceeds without the need for any dose modification as described in Section 5.2.1.2.1, Imprime PGG will be administered to all subjects at a dose of 4 mg/kg IV over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle. Refer to Appendix 14.1 for further details.

If enrollment into an additional cohort in Stage 1 is necessitated based on the dose modification requirements as described in Section 5.2.1.2.1, Imprime PGG will be administered to all subjects in the specified indication at a dose of 2 mg/kg IV over a 2-hour infusion time period on Day 1, Day 8, and Day 15 of each 3-week cycle. Refer to Appendix 14.1 for further details.

Imprime PGG must always be administered first, with a 15-30 minute window before the start of the pembrolizumab infusion.

The pembrolizumab fixed dose of 200 mg will be administered IV over 30 minutes on Day 1 of each 3-week treatment. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

5.2.3 Trial Blinding/Masking

Subjects in this study will not be blinded, as all subjects will receive identical treatment.

5.3 Randomization or Treatment Allocation

Neither randomization nor treatment allocation is required in this study, as all subjects will receive identical treatment.

5.4 Stratification

There will be no stratification in this study.

5.5 Numbers of Sites and Subjects and Study Duration

5.5.1 Number of Sites

It is anticipated there will be approximately 25 sites within the United States. Additional regions, countries, or sites may be added as needed.

Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.5.2 Number of Subjects

The individual patients in this clinical trial will be referred to as "subjects".

It is anticipated there will be approximately up to N=94 subjects in total, distributed in the following manner between melanoma and TNBC subjects:

1. Up to N = 41 subjects with melanoma (up to 24 in total in Stage 1 and 17 in Stage 2)
2. Up to N = 53 subjects with TNBC (up to 24 in total in Stage 1 and 29 in Stage 2)

Please refer to Section 5.9 on Subject Replacement Strategy for further information on the replacement of subjects who do not complete the study.

5.5.3 Study Duration

Study duration for a subject may last approximately 3 years comprising of the following:

- Screening: Up to 90 days
- Treatment Phase: Up to 2 years
- Survival Follow-up: Up to 1 year

The actual study duration for any individual subject may be shorter or longer than what is listed above, depending on when the subject enrolled during the overall life of the study, and the subject's individual situation.

5.6 Concomitant Medications/Vaccinations (Allowed and Prohibited)

Subjects should be treated for any concurrent medical conditions at the discretion of the Investigator according to community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination 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. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

Other than Imprime PGG or pembrolizumab, any medication administered to the subject during any portion of the study after study treatment is initiated on Cycle 1/Day 1 is considered a concomitant medication and must be documented in the electronic Case Report Form (eCRF). This includes all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids.

Medications administered during the Screening period should be recorded as prior medications on the eCRF.

5.6.1 Acceptable Concomitant Medications

Most concomitant medications, including pretreatment with anti-emetics, anti-diarrheals, and anti-histamines are permitted and may be administered at the Investigator’s discretion.

5.6.2 Prohibited Concomitant Medications

The Sponsor or designee should be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Continued participation of the subject will be at the discretion of the Sponsor.

Medications or vaccinations contraindicated for use in combination with pembrolizumab include those listed in the exclusion criteria should not be administered. If there is a clinical indication for a medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the local Clinical Monitor.

Following is a list of therapies subjects are prohibited from receiving at any point during this clinical study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or Imprime PGG
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with Sponsor. The subject must have clear measurable disease outside the radiated

field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- 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 (eg, 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.
  Note: Inhaled steroids are allowed for management of asthma

In addition, no additional investigational agents are to be administered during the study. In the event a subject develops neutropenia, GCSF administration is allowed (to be administered per ASCO guidelines and/or the site's standard of care).

Subjects who have received palliative radiotherapy for pain will be assessed during the data analysis phase to determine if their data may be assessed with that of other subjects, or if their data should be truncated at the time of receiving the radiotherapy with data extrapolated for all remaining visits as the response assessment may be affected.

There are no prohibited therapies Post-Treatment, however any such therapies must be recorded during the time the subject is being followed for OS.

5.6.3 Supportive Care Guidelines

Imprime PGG supportive care guidelines should follow the ASCO Clinical Practice Guidelines.

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 below, along with the dose modification guidelines presented earlier in Section 5.2.1.2.2 in Table 1. 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 to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Section 5.2.1.2.2 for guidelines regarding dose modification and supportive care.

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

See Section 5.2.1.2.2 for treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

It is unknown what the effects of Imprime PGG may be during a pregnancy.

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.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they:

(1) Are postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.)

OR

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening

OR

(3) Have a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) Practice abstinence[†] from heterosexual activity;

OR

(2) Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are the following‡:

- Single method (1 of the following is acceptable):
    - Intrauterine device (IUD)
    - Vasectomy of a female subject's male partner
    - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
    - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - Cervical cap with spermicide (nulliparous women only)
    - Contraceptive sponge (nulliparous women only)
    - Male condom or female condom (cannot be used together)
    - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with either Imprime PGG or pembrolizumab, 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 the Sponsor without delay and within 24

hours if the outcome is a serious adverse experience (eg, 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 the Sponsor.

5.7.4 Use in Nursing Women

It is not known whether either Imprime PGG or pembrolizumab 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 into the study.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Withdrawal/Discontinuation Criteria

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time without prejudice to future care. The Investigator will provide a written report describing the reason for discontinuation. If a subject discontinues study drug, every effort should be made to complete the assessments scheduled to occur during the Post-Treatment Visit and survival follow-up period. The subject will continue to be followed until completion of the study.

A subject may discontinue study drug for the following medical or administrative reasons:

- Adverse event: If a subject suffers an AE that in the judgment of the Investigator, presents an unacceptable consequence or risk to the subject, the subject may be discontinued from study drug
- Progressive Disease per irRECIST (see Section 7.3.2)
- Subject decision: A subject may voluntarily discontinue from study drug at any time
- Intercurrent illness: A subject may discontinue study drug if, in the judgment of the Investigator, the subject develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal from the study drugs, or that requires treatment with a restricted medication.
- Ineligibility to protocol entry criteria determined
- Lost to follow-up
- Administrative discontinuation: After consultation between the Investigator, the medical monitor, or the Sponsor when appropriate, a subject may be discontinued from study drug for the following administrative reasons:
    - Noncompliance (all occurrences of noncompliance must be documented on the appropriate eCRFs)

- Failure to receive study drug per protocol as defined in Section 5.2 Trial Treatments
- Failure to comply with protocol requirements
- Refusal of study drug administration (with reason documented)

In all cases, when subjects discontinue study drug, reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments following such discontinuation. These efforts should be documented on the appropriate eCRF. The subject will continue to be followed for survival for the duration of the study.

If a subject withdraws consent for follow-up of survival, this must be documented, and no further efforts at contact will be attempted.

5.8.2 Discontinuation of Study Therapy After Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR, who have been treated for at least 24 weeks, and who had at least 2 treatments with study medications beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 1 year of additional treatment with Imprime PGG + pembrolizumab at the discretion of the Investigator if:

- No cancer treatment was administered since the last dose of pembrolizumab
- The subject meets the safety parameters listed in the Inclusion/Exclusion criteria
- The trial is open

Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Response or progression in this resumed course of therapy will not count towards the ORR of the primary endpoint in this trial.

5.9 Subject Replacement Strategy

Subjects who discontinue the study treatment due to reasons other than progressive disease or treatment-related adverse events before the first post-baseline scan may be replaced.

5.10 Clinical Criteria for Early Trial Termination

If the Sponsor, Investigator, medical or safety monitor, or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or the study site should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, regulatory, and medical and safety monitors.

Conditions that may warrant early termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to enrolled subjects

- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

Other conditions that may also warrant termination of an individual study site include, but are not limited to, the following:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the research facility to the Sponsor, clinical research associate (CRA), medical and/or safety monitor(s), or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the guideline provided by ICH for Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice (ICH GCP): Consolidated Guideline (E6), Sections 4.12, 4.13, 5.20, and 5.21.

6.0 TRIAL FLOW CHART

6.1 Schedule of Assessments - Study Flow Chart

Cycle		C1	C2	C3	C4	C5	C6	C7 and QOC	C8 and Q4C (C12, C16, C20, C24, C28, C32)	C10 and Q4C (C14, C18, C22, C26, C30, C34)	End of Treatment (EOT)		Post-Treatment (up to 3 Years after Last Subject's 1st Dose)
Visit Week	Screening (-30 to -1 Days)*	W1	W4	W7	W10	W13	W16	W19 and Q6W	W22 and Q12W (W34, W46, W58, W70, W82, W94)	W28 and Q12W (W40, W52, W64, W76, W88, W100)		30-Day SFU	
Administrative Procedures													
Informed Consent	X												
Review of Entry Criteria	X												
Urine Pregnancy	X											X	
Medical Hx and Demography	X												
Enrollment	X												
Clinical Procedures / Assessments													
ECOG Status	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X										X		
Vital Signs	X												
Weight	X	X	X	X	X	X	X	X	X	X	X		
AE Monitoring (Every Visit in Cycle)	X	X	X	X	X	X	X	X	X	X	X	X	
Administration of Pembrolizumab (D1 of Each Cycle)		X	X	X	X	X	X	X	X	X			
Administration of Imprime PGG (D1, D8, D15 of Each Cycle)		X	X	X	X	X	X	X	X	X			
Concomitant Medications (Every Visit in Cycle)		X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures / Assessments													
Hematology**	X*	X	X	X	X	X	X	X	X	X	X	X	

Cycle		C1	C2	C3	C4	C5	C6	C7 and QOC	C8 and Q4C (C12, C16, C20, C24, C28, C32)	C10 and Q4C (C14, C18, C22, C26, C30, C34)	End of Treatment (EOT)		Post-Treatment (up to 3 Years after Last Subject's 1st Dose)
Visit Week	Screening (-30 to -1 Days)*	W1	W4	W7	W10	W13	W16	W19 and Q6W	W22 and Q12W (W34, W46, W58, W70, W82, W94)	W28 and Q12W (W40, W52, W64, W76, W88, W100)		30-Day SFU	
CBC/Differential (Pre-Imprime infusion and 4 Hr Post-SOI of Imprime: Q4C after C2, EOT)*		X	X				X			X	X		
PBMC (Pre-Imprime infusion and EOI of Imprime: C1, C2, C6, EOT)		X	X				X				X		
RNA/DNA (Pre-Imprime infusion and EOI of Pembro: Q4C after C2, EOT)		X	X				X			X	X		
Serum Chemistry° (QOC, EOT, SFU)	X*	X		X		X		X			X	X	
Coagulation Tests	X*												
Serum ABA (Pre-Imprime Infusion and EOI of Imprime: Q4C after C6, EOT)	X (within 90 days)	X	X	X	X	X	X			X	X		
Serum Cytokines & Complement (Pre-Imprime Infusion and EOI of Imprime: Q4C after C6, EOT)		X	X	X	X	X	X			X	X		
PK (C1, C3 only)		X		X									
Urinalysis	X												
12-Lead ECG	X												
Efficacy Measurements													
CT Scan with Contrast or MRI (Q6W/QOC)	X		X (C2 end)		X (C4 end)		X (C6 end)		X (Cycle end)	X (Cycle end)			

Cycle		C1	C2	C3	C4	C5	C6	C7 and QOC	C8 and Q4C (C12, C16, C20, C24, C28, C32)	C10 and Q4C (C14, C18, C22, C26, C30, C34)	End of Treatment (EOT)		Post-Treatment (up to 3 Years after Last Subject's 1st Dose)
Visit Week	Screening (-30 to -1 Days)*	W1	W4	W7	W10	W13	W16	W19 and Q6W	W22 and Q12W (W34, W46, W58, W70, W82, W94)	W28 and Q12W (W40, W52, W64, W76, W88, W100)		30-Day SFU	
Tumor Biopsies													
Archival Biopsy (if feasible) (Sample 1)	X												
Biopsy before First Dose of Treatment (if feasible) (Sample 2)		X											
Biopsy after C2 Complete but before C3 Dosing (if feasible) (Sample 3)				X									
Biopsy at Time of Response or Progression, or EOT (if feasible) (Sample 4)											X		
Long-Term Follow-up													
Survival Monitoring (Up to 3 Years After Last Subject's 1st Dose)													X

*Screening window is 15 days before start of dosing for the following Inclusion Criteria: Organ, Renal, Hematologic, and Coagulation Functions

° Serum Chemistry includes Thyroid Function Panel

**Hematology results may be used without the need for an additional blood draw if Hematology is drawn within approximately 1 hour before start of Imprime PGG infusion

Monthly pregnancy testing should be conducted as per local regulations where applicable.

Note: C = Cycle
W = Week
D8 = Day 8
D15 = Day 15
EOI = End of Infusion of Imprime PGG (unless pembrolizumab has been specified) (Samples collected EOI should be within approximately 30 minutes after infusion ends)
EOT = End of Treatment
Pre-infusion = Before start of Imprime PGG infusion (Samples collected Pre-infusion should be within approximately 1 hour before start of infusion)
SOI = Start of Infusion of Imprime PGG
QOC = Every Other Cycle
Q4C = Every 4th Cycle
Q6W = Every 6 weeks
Q12W = Every 12 weeks

Cycle Assessments:

- C1, C2, C3, C4, C5, C6, EOT, 30-Day SFU, and Post-Treatment are as indicated in the table above
- C7, C9, C11, C13, C15, C17, C19, C21, C23, C25, C27, C29, C31, C33, and C35 have identical assessments
- C8, C12, C16, C20, C24, C28, and C32 have identical assessments
- C10, C14, C18, C22, C26, C30, and C34 have identical assessments

7.0 TRIAL PROCEDURES

Table 6.1, Schedule of Assessments – Study Flow Chart, summarizes the frequency and timing of study activities and assessments from Screening through the end of the study and Post-treatment Visits (30-Day Safety Follow-up (SFU) Visit and monitoring for overall survival). Visits should occur as scheduled in Table 6.1 to the extent possible.

7.1 Visit Windows

All treatment visits should occur on the visit days specified in Table 6.1, Schedule of Assessments. However the following visit windows, while not desirable, are acceptable:

- For study medication administration, a visit window of +/- 3 days
- For hematology and chemistry laboratories, a visit window of - 3 days
- For imaging, a visit window of +/-7 days (which should follow calendar days and not be adjusted for cycle delays)
- For the End of Study Visit, a visit window of +3 days
- For the 30-Day SFU Visit, a visit window of -7 days
- For Every-2-Month Survival Monitoring, a visit window of +/- 7 days

7.2 Screening Period

Prior to any study-specific assessments or Screening procedures, a written, signed ICF will be obtained from subjects. A copy of the signed ICF will be provided to the subject.

A Screening examination should be performed between 1 and 30 days before the first day of treatment to determine study eligibility. Subjects who meet all entry criteria will be enrolled into the study.

A Screen Failure Log must be maintained by the Investigator for all screened subjects.

A subject may be re-screened an additional 2 times if entry criteria are not met, as long as this occurs within 90 days of the signing of the ICF.

7.3 Treatment Period (Treatment Cycles)

Study Day 1 is defined as the day of the first dose of study medication.

The study treatment period will be divided into treatment cycles. Each cycle will be 3 weeks in duration and defined by the frequency of pembrolizumab administration. During each cycle, subjects will dose weekly with Imprime PGG for all 3 weeks (Days 1, 8, and 15). Pembrolizumab will be dosed on D1 of each 3-week cycle. Subjects will be dosed until

disease progression or death or study termination or 2 years or until any of the criteria for study drug discontinuation are met (whichever occurs first).

See Section 5.2.2 Timing of Dose Administration for the order in which the study medications must be administered.

7.3.1 Clinical Assessments and Procedures

7.3.2 Tumor Response Criteria

Tumour response will be evaluated according to the RECIST v1.1 (see Appendix 14.5) (http://www.eortc.be/Recist/documents/RECISTGuidelines.pdf) and clinical criteria (Eisenhauer et al, 2009). Disease progression will be defined as per RECIST version 1.1 guidelines on radiological, clinical, or symptomatic progression.

Evaluation of response by RECIST v1.1 criteria should be performed at baseline and then at 6-week intervals beginning at Week 6. Immune-related response criteria (irRECIST) (see Appendix 14.6) may be used for clinical management of subjects, but will not be used for OR evaluation (other than as an exploratory endpoint). Therefore RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with immunotherapy treatment. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging verifies initial PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment per the conditions stated below, while awaiting radiologic confirmation of progression.

If repeat imaging shows < 20% or < 5 mm absolute increase in tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed.

If repeat imaging confirms PD due to any of the scenarios listed below, subjects will be discontinued from study treatment*.

In determining whether or not the tumor burden has increased or decreased, the Investigator should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir

- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

In subjects who have initial evidence of radiological PD, it is at the discretion of the subject and the Investigator whether to continue a subject on study treatment until repeat imaging is obtained:

- The subject must re-consent to the study, in order to continue receiving study medication in light of the radiological evidence of PD.
- The Investigator's clinical judgment decision regarding the subject continuing should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Subjects may receive study treatment while waiting for confirmation of PD if they have re-consented and are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until PD has been confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

*Note: If PD is confirmed but the subject is experiencing an extraordinary clinical benefit, contact Sponsor to discuss continuing treatment.

All RECIST assessments (v1.1 or irRECIST) will be evaluated against the initial lesion measurement values from the baseline computed tomography (CT) scan or magnetic resonance imaging (MRI) obtained prior to the initiation of study treatment. Either CT or MRI is acceptable, but the same method must be used throughout the study for any individual subject. If MRIs are used, they must include images of the head, chest, abdomen, and pelvis.

7.3.3 Tumor Imaging

Tumor imaging should be performed by CT (preferred). MRI should only be used when CT is contraindicated or for imaging in the brain, but the same imaging technique should be used in a subject throughout the trial. A CT scan is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized if clinically appropriate.

Imaging should include the chest, abdomen, and pelvis.

For TNBC subjects, bone scans will also be utilized to assess osseous metastases. Additionally, X-ray evaluation will be obtained for symptomatic sites with negative bone scan evaluations. The sponsor should be notified of any supplemental imaging done to support a positive or negative bone scan.

7.3.3.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of first dose of trial treatment. The Investigator must review screening images to confirm the subject has measurable disease per RECIST v1.1.

Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to the start of study treatment and viewed by the Investigator.

7.3.3.2 On Study Tumor Imaging

The first on study imaging assessment should be performed 6 weeks (±7 days) from the date of first dose of trial treatment. Subsequent tumor imaging should be performed every 6 weeks (±7 days) or more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of study medication cycle intervals.

Per RECIST v1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie 6 weeks later), whichever is clinically indicated.

Continue to perform imaging until whichever of the following occurs first:

- Disease progression
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- End of the study

7.3.4 RECIST Assessment of Disease

RECIST v1.1 will be applied by the Investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status.

irRECIST will applied by the Investigator solely for clinical management of subjects, as described in Section 7.3.2 and in Appendix 14.6.

7.3.5 Tumor Biopsy Samples

Tumor biopsy information must be collected for this study as follows:

1. An official diagnostic pathology report +/- archival tumor biopsy sample (in order to be eligible for the study)

An additional 3 tumor biopsy samples, preferably obtained from the same localized region, are highly desirable when feasible and are as follows:

2. Sample before the first dose of study treatment (which will also be used for PD-L1 biomarker analysis)
3. Sample after Cycle 2 is completed but before initiation of Cycle 3 dosing (which will also be used for PD-L1 biomarker analysis)
4. Sample either at the time of response or at the End of Study Visit (if no response).

Note that for Sample 2 and Sample 3, the following condition must be met:

- The tumor tissue sample for PD-L1 biomarker analysis should be from a newly obtained core or excisional biopsy. Repeat samples may be required if adequate tissue is not provided. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut.
- Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date, otherwise a new specimen will be requested.

7.3.6 Physical Examination and Measurement of Vital Signs

Vital signs will be measured on all subjects at Screening.

Subjects will undergo a complete physical examination (including observable tumor measurements) at the Screening and at the End of Study Visits.

Weight will be taken at Screening, on Day 1 of every 3-week treatment cycle before study drug is administered, and at the End of Study Visit.

7.3.7 Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 14.3). It is recommended, whenever that the subject be assessed by the same person throughout the study.

Performance status will be assessed at Screening, on Day 1 of every 3-week treatment cycle before study drug is administered, at the End of Study visit, and at the 30-Day Safety Follow-up (SFU) visit.

7.3.8 Clinical Safety Assessments

The NCI CTC-AE version 4.03 will be used to evaluate the clinical safety of the treatment in this study. Subjects will be assessed for AEs at each clinical visit and as necessary throughout the study.

7.3.9 Planned DNA and RNA Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

In addition to studying variation across the human genome, RNA expression profiles may be investigated.

7.3.10 Laboratory Assessments

Laboratory safety assessments will be performed at the timepoints specified in Section 6.1 Schedule of Assessments. All laboratory testing will be conducted via local laboratories. Normal ranges for the study laboratory parameters must be supplied to Biothera before study start by each investigational site.

Samples for PBMC, RNA, DNA, Serum ABA, Serum Cytokines, Serum Complement and inflammation markers, and potentially other serum proteins, will be collected by the central laboratory for conduct of the assays.

Please refer to Table 3 below for the analytes to be collected in this study:

Table 3. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal results noted)*	PK
Absolute Neutrophil Count	Carbon Dioxide ‡ *(CO_2 or biocarbonate)*	Urine pregnancy test †	PBMC
	Uric Acid		Serum ABA
	Calcium		Serum Cytokines
	Chloride		RNA
	Glucose		PD-L1
	Phosphorus		DNA
	Potassium		Serum complement and inflammation markers
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above ULN)*		
	Total protein		
	Blood Urea Nitrogen		
	Thyroid Function Panel		
	• Total triiodothyronine (T3) or (FT3)		
	• Free thyroxine (FT4)		
	• Thyroid stimulating hormone (TSH)		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

7.3.11 Pharmacokinetic Evaluations

Samples for sparse PK will be taken at specified times (please refer to Table 4) for all subjects on Cycle 1/Day 1 and on Cycle 3/Day 1.

See Section 5.2.2 Timing of Dose Administration for the order in which the study medications must be administered.

Table 4. Time and Events for Sparse PK Collection

Time (Hours)	All Subjects	
	Cycle 1/Day 1	Cycle 3/Day 1
Imprime PGG Infusion		
Pre-dose	X	X
0		
1.5 hrs (±30 min) post end of Imprime infusion	X	X
Pembrolizumab Infusion		
Pre-dose	X	X
0		
3 hrs (±30 min) post end of pembrolizumab infusion	X	X

7.3.12 Unscheduled Visits

Additional visits may be scheduled per the Investigator discretion if the subject's medical condition warrants, ensuring his/her safety and well-being. Any additional visits, examinations, or procedures must be documented.

7.4 Post-treatment Assessments

7.4.1 End of Treatment/End of Study Visit

Study drug will be discontinued upon disease progression, development of study withdrawal criteria, duration of 2 years in the study, or study closure. Subjects deriving clinical benefit from the administration of Imprime PGG + pembrolizumab and who have completed 2 years of study treatment may be candidates for continued treatment after discussion between the subject, Investigator, and Sponsor.

The End of Treatment Visit (EOT) should occur as soon as possible after the end of the cycle in which the last administration of study drug occurred (window of +3 days). During this visit, the following assessments will occur:

- ECOG Performance Status Score
- Physical examination
- Weight
- Adverse events recording
- Concomitant medications recording
- Hematology
- CBC/Differential*
- RNA/DNA*
- Chemistry
- Serum ABA*
- Serum cytokines, serum complement, and inflammation markers*
- If feasible, the fourth and final biopsy sample (unless it was collected earlier at time of response or progression)

* Only collected once (instead of at both Pre-infusion and Post-infusion as at other visits as no study medication is administered at this visit)

7.4.2 30-Day Safety Follow-up Visit (30-Day SFU)

The 30-Day SFU visit will occur within 4 weeks (window of -7 days) of study drug dosing being stopped. During this visit, the following assessments will occur:

- ECOG Performance Status Score
- Pregnancy test for women of childbearing potential
- Adverse event recording
- Concomitant medications recording
- Hematology
- Chemistry

7.4.3 Every 2-Month Overall Survival Monitoring

Upon completion of the 30-Day SFU visit, subjects will be monitored on an every 2-month visit schedule for survival until death or until study completion. Study completion is defined as the death of at least 70% of subjects or 3 years after the last subject's first dose, whichever occurs earlier.

Only survival status and start of any new anti-cancer therapy will be collected during this period.

Subjects who discontinue study drug without evidence of PD per RECIST v1.1 will have CT scans or MRI every 6 weeks during the survival-monitoring period to determine disease status until PD.

8.0 ADVERSE EVENTS (SERIOUS AND NON-SERIOUS)

8.1 Non-serious Adverse Events

8.1.1 Definition of Adverse Event and Non-serious Adverse Event

The following definition of adverse event will be used for the study:

> Any untoward medical occurrence in a study subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to medicinal (investigational) product.

This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline. Disease progression, and events caused by disease progression, will be considered an efficacy endpoint and should not be reported as an AE, even if the event results in hospitalization. Therefore progression of the cancer under study is not considered an adverse event.

A "non-serious" AE is any event that does not meet the definition of "serious adverse event" (SAE) as presented in Section 8.2 below.

8.1.2 Reporting and Treating Non-serious Adverse Events

It is the responsibility of the Investigator to perform regular assessments for AEs. Subjects will be regularly queried about the occurrence of any AEs and will be monitored throughout the study for reactions to study drug and/or study procedures. The Investigator and clinical staff will record all AEs, whether volunteered by or elicited from the subject, at anytime

during a subject's participation in the study. All events occurring prior to the first dosing will be recorded on the Medical History eCRF, except an SAE leading to exclusion from the trial or as a result of a protocol-specified intervention as described in Section 8.2.2, will be recorded on the Adverse Event eCRF. All AEs occurring at any time after the initiation of the first dose of study drug up to 30 days following the last dose of study drug will be recorded on the Adverse Event eCRF. Adverse events will be recorded according to the CTCAE v4.03 (Appendix 14.4). Adverse events meeting the definition of SAE require additional reporting as described in the following section.

All subjects experiencing an AE will be evaluated by the Investigator and monitored until resolution of the event or until the Investigator deems the event clinically stable and/or at an acceptable level. Unless the event requires hospitalization (SAE), medical treatment will be provided to the subjects at the unit, and treatment medication and/or medical procedures will preferably be provided under the guidance of the treating-Investigator's clinical discretion. All AEs, including clinically significant laboratory abnormalities, will be followed until resolution. Serious adverse events require special reporting in addition to documentation in the eCRF as described in the section on Serious Adverse Events.

It is the Investigator's responsibility to provide his/her assessment of the relationship of the event to the study drug and the severity of the event using the following scales:

- Relationship
    - No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected
    - Yes – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified
- Severity

  The severity of all AEs should be graded according to the CTCAE v4.03. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those AEs not listed in the CTCAE, the following grading system should be employed:

    - Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities
    - Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable
    - Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable

- Life-threatening (CTCAE Grade 4): Life-threatening of disabling adverse event
- Death (CTCAE Grade 5): Death-related adverse event. See CTCAE Guidelines for assigning Grade 5.

8.2 Serious Adverse Events

8.2.1 Definition of Serious Adverse Event

The following definition of SAE applies for the study:

> An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:
>
> - Death
> - Life-threatening AE
> - Inpatient hospitalization or prolongation of existing hospitalization
> - Persistent or significant disability/incapacity
> - Congenital anomaly/birth defect
>
> Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is any AE that places the subject or subjects, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (eg, it does not include a reaction that, had it occurred in a more severe form, might have caused death).

In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs in order to meet certain local requirements.

Therefore, the following events are considered serious by the Sponsor for collection purposes:

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

8.2.2 Reporting and Treating Serious Adverse Events

An AE that is serious (SAE) requires additional detailed reports and follow-up. The content of these detailed reports must address the Investigator's estimate of causality and must provide the information specified in the SAE Report Form and International Conference on Harmonisation (ICH) guidelines, in so far as is possible.

For the time period beginning when the consent form is signed until treatment enrollment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at treatment enrollment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to the Sponsor's products, must be reported within 24 hours to the Sponsor.

Additionally, any serious adverse event, considered by an Investigator who is a qualified physician to be related to the Sponsor's products that is brought to the attention of the Investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph, also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

Following is the safety contact information for reporting serious adverse events worldwide:

Safety Contact Information
SAE Hotline: +01 609.531.0476
Facsimile: +01 609.531.0154
E-mail: safety.biothera@apcerpharma.com

The Investigator will be requested to supply detailed information regarding the event. All serious and unexpected AEs/SAEs must also be reported to the reviewing IEC/IRB as per specific requirements and a copy of that report must be retained at the investigative site and filed in the Investigator Site File.

Death due to any cause occurring >30 days after the last dose of study drug during the survival-monitoring period will not be reported as an adverse event. Disease progression will not be reported as an AE/SAE.

Each Investigator is responsible for reporting adverse events observed with concomitant medications per his/her region’s respective regulatory guidelines.

8.3 Definition of an Overdose for This Protocol and Reporting of Overdose

For purposes of this trial, an Imprime PGG overdose will be defined as any Imprime PGG dose > 6 mg/kg (50% increase).

For purposes of this trial, a pembrolizumab overdose will be defined as any pembrolizumab dose ≥ 1000 mg (5 times the dose).

There have been no known reports of overdose of Imprime PGG. No specific information is available on the treatment of overdose of either Imprime PGG or pembrolizumab. In the event of overdose, study medication should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

All reports of overdose with and without an adverse event must be reported within 24 hours of the Investigator's knowledge of the event to the Sponsor.

8.4 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) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment enrollment must be reported by the Investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

Pregnancies and lactations that occur from the time of treatment enrollment through 120 days following cessation of Sponsor's products, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies 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 adverse events. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within one (1) working day of the Investigator becoming aware of the event.

8.5 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment enrollment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

For the time period beginning at treatment enrollment through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's products, must be reported within 24 hours to the Sponsor.

Events of clinical interest for this trial include:

1. Overdose of Sponsor's products, as defined in Section 8.3 Definition of an Overdose for This Protocol and Reporting of Overdose, that is not associated with clinical symptoms or abnormal laboratory results
2. Elevated AST or ALT laboratory value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value ≥ 2X the ULN and at the same time, an alkaline phosphatase laboratory value < 2X the ULN, 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.

All ECIs should be reported to the sponsor within 24 hours of the Investigator's knowledge of the event.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below.

9.1.1 Hypothesis and Study Design

The study design is based on hypothesis testing of the ORR for pembrolizumab + Imprime PGG. For melanoma subjects, the null hypothesis is ORR ≤ 5%, versus the alternative hypothesis of ORR ≥ 23%; for the TNBC subjects, the null hypothesis is ORR ≤ 5% (ORR=5% in KEYNOTE-086), and the alternative hypothesis is ORR ≥ 21%. Hypotheses testing will be conducted using a one-sided type I error of 0.05.

The study will incorporate Simon's optimal 2-stage design with sample size fixed at 12 subjects in Stage 1 (for melanoma, Simon's optimal 2-stage design has 12 subjects at Stage 1; for TNBC, a modified Simon's 2-stage design with the sample size fixed at 12 at Stage 1 is used). The safety criterion of ≤ 4 (or ≤ 33%) subjects with Grade 3/4 adverse events in Cycle 1 within either tumor type must be met in order to proceed to Stage 2. The starting dose is 4 mg/kg for Imprime PGG. In the event there are a total of > 4 (or > 33%) of subjects with Grade 3/4 adverse events in Cycle 1, the dose of Imprime PGG will be reduced to 2 mg/kg, and Stage 1 will be repeated at a dose of 2 mg/kg with an additional cohort of n=12 subjects. For the dose that meets the safety criterion in Stage 1, at least 1 response in

melanoma subjects and 1 response in TNBC subjects amongst the 12 subjects within each tumor type must be observed in order to proceed to Stage 2. The probabilities of early termination at Stage 1 for not achieving such responses are 0.54 and 0.54 if the null hypothesis is observed for melanoma and TNBC subjects, respectively. Stage 2 will enroll an additional 17 subjects with melanoma and 29 subjects with TNBC.

For the dose that meets the safety criterion in Stage 1, rejection of the null hypothesis will require documenting at least 4 objective responses among the total of up to 29 subjects with melanoma and 5 objective responses among the total of up to 41 subjects with TNBC.

The above designs correspond to a type I error 0.05 and power of 90% for both melanoma and TNBC. The PASS 14 Power Analysis and Sample Size System statistical software was used for the study design calculation.

9.1.2 Sample Size

The planned sample size for melanoma is up to 41 subjects with up to 24 subjects for Stage 1 and 17 subjects for Stage 2; the planned sample size for TNBC is up to 53 subjects with up to 24 subjects for Stage 1 and 29 subjects for Stage 2.

9.1.3 Efficacy Analyses

Efficacy analysis will be conducted separately for each tumor type. The primary efficacy endpoint is ORR, and the secondary efficacy endpoints include PFS, TTR, CRR, DoR and OS. The primary efficacy population will include all evaluable subjects who receive at least one dose of study treatment, have measurable disease at baseline per RECIST v1.1, and have at least one post-baseline scan or discontinue study treatment as a result of progressive disease, death, or a treatment-related adverse event before the first post-baseline scan.

Hypotheses testing of ORR will be conducted among evaluable subjects at the dose which meets the safety criterion in Stage 1. Among the 12 evaluable subjects in Stage 1, at least 1 objective response in melanoma subjects would be needed to proceed to Stage 2 for melanoma; and at least 1 objective response in TNBC subjects would be needed to proceed to Stage 2 for TNBC. If there are at least 4 objective responses among the total of 29 evaluable subjects with melanoma and/or at least 5 objective responses among the total of 41 evaluable subjects with TNBC, the null hypothesis will be rejected for melanoma and/or TNBC and the study will be declared a success.

The point estimate along with the exact 95% confidence interval will be computed for ORR and CRR. PFS and OS will be summarized descriptively and graphically using the Kaplan-Meier method. The Kaplan-Meier estimate for the median, first, and third quartiles will be determined along with 95% confidence intervals (CIs). The Brookmeyer-Crowley method will be used for the CI calculations. For the subset of subjects who have a CR or PR, TTR and DoR will be summarized similarly using the Kaplan-Meier method. The Kaplan-Meier

estimate of PFS rate at the landmark times of 6 months and 1 year, and the OS rates at the landmark time of 1 year will be calculated.

Exploratory analyses may be conducted using iRECIST.

9.1.4 Safety Analyses

Safety analysis will be conducted separately for each tumor type. All subjects who receive at least 1 dose of study treatment will be included in the safety analysis. Adverse events by maximum toxicity grade will be summarized with frequency/proportion of total subjects by system organ class and preferred term. Separate summaries will be provided for all adverse events, drug-related adverse events, serious adverse events, and adverse events leading to discontinuation of study treatments. The incidence of deaths and the primary cause of death will be summarized. Hematology and clinical chemistry data will be summarized by worst-case toxicity grade shift from baseline. The results of other safety measurements (eg, ECOG performance status) will also be summarized.

9.1.5 PK Analyses

The PK analyses will be based on the PK population. The PK concentration data will be listed and summarized by planned visit/time.

9.1.6 Interim Analyses

One interim analysis will be conducted at the end of Stage 1 for each tumor type. For the dose which meets the safety criterion in Stage 1, if at least 1 objective response among 12 evaluable melanoma subjects is not observed, the melanoma cohort will be terminated; if at least 1 objective response among 12 TNBC evaluable subjects are not observed, the TNBC cohort will be terminated. Early stopping at the interim analysis will only occur for futility, not efficacy. Adverse events including ≥ Grade 3 events will be summarized at the time of the interim analysis.

9.2 Statistical Analysis Plan

A detailed Statistical Analysis Plan will be developed as a separate document for this protocol.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product Identification and Description

10.1.1 Imprime PGG

Imprime PGG will be provided by Biothera as a preservative-free, sterile, formulation in 20 or 50-mL clear borosilicate vials. Each vial will contain active ingredient at a nominal concentration of 1.0 mg/mL in 140 mM sodium chloride, 11 mM sodium citrate, at pH of 5.0 to 7.5. Vials are filled to a target volume of 21.2 or 52.0 mL respectively, to ensure a deliverable amount of 20 or 50 mL respectively. The active ingredient under investigation is β(1,6)-[poly-(1,3)-D-glucopyranosyl]-poly-β(1,3)-D-glucopyranose (PGG beta glucan) derived from a proprietary, nonrecombinant strain of *Saccharomyces cerevisiae* and has an average molecular weight of 120,000 to 205,000 Daltons. The vehicle used to dilute Imprime PGG is 0.9% sodium chloride for injection. Each individual clinical study site will supply its own vehicle.

Imprime PGG will be individually labeled in accordance with local regulations. A label will be affixed to the vial with the following information.

Protocol: BT-CL-PGG-XXXXXXX Imprime PGG Injection (i.v.) 50mL (1mg/mL), Lot#: xxxxx Expiry: 50mg solution, dilute, infuse as directed Store at 20ºC - 25ºC- Do not freeze Biothera, Eagan, MN 55121 USA Caution: New drug- Limited by Federal (or United States) law to investigational use	Protocol: BT-CL-PGG-XXXXXXX Imprime PGG Injection 50mL (1mg/mL), Lot#: xxxxx Subject number: _____ Site/Investigator: _____ Date dispensed: _____ Dispensed by: _____ Biothera, Eagan, MN 55121 USA Investigator: _____

10.1.2 Pembrolizumab

For a complete description of pembrolizumab, please refer to the pembrolizumab regional prescribing guidelines (see Appendix 14.2).

In summary, pembrolizumab for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). It may contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab will be provided by the Sponsor as summarized in Table 5.

Table 5. Pembrolizumab Product Description

Product Name and Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

10.2 Storage and Handling of Clinical Study Material

10.2.1 Storage and Handling of Imprime PGG

Imprime PGG vials will be provided to the investigative site. Vials must be stored at controlled room temperature that encompasses the usual and customary working environment of 20ºC - 25ºC upon arrival at the site. 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 and note any discrepancies or damages. Lot numbers and vial counts should be entered into the EDC.

10.2.2 Storage and Handling of Pembrolizumab

Please refer to the pembrolizumab regional prescribing guidelines for a comprehensive discussion on the storage and handling of pembrolizumab (see Appendix 14.2).

10.3 Preparation, Dosing Instructions, and Schedule

The clinical study site's pharmacist or the study Investigator will be responsible for the preparation of all study medications: Imprime PGG and pembrolizumab. All subjects will receive Imprime PGG prior to pembrolizumab. The compounds should be administered consecutively, at least 15 minutes apart (but no more than 30 minutes).

Instructions for the proper mixing and administration of Imprime PGG can be found in Appendix 14.1 on Imprime PGG Preparation and Dosing Instructions. A low protein binding 0.22-micrometer inline filter should be utilized during administration of Imprime PGG.

Instructions for the proper mixing and administration of pembrolizumab can be found in the regional prescribing guidelines for pembrolizumab.

Other drugs should not be added to the infusion mixtures, and IV lines should be flushed as per standard practice between infusions. Care should be taken to avoid extravasation at the infusion site. The infusion site should be monitored frequently for signs of inflammation.

The dosing schedule is presented in Table 6.1 in the Schedule of Assessments.

10.4 Premedications

Each cycle will be 3 weeks in duration. During this time, subjects may receive pre-treatment with standard anti-histamine medications before commencing dosing of study medications on each treatment day and, as needed, post-dose.

Premedications:

- Cycle 1/Day 1: Pretreat with an H1 antagonist (eg, 50 mg of diphenhydramine IV).
- Subsequent cycles: Premedication is allowed for each Imprime PGG infusion, but if tolerated by the subject, reduced premedication doses from those administered at Cycle 1/Day 1 should be used.

10.5 Preparation and Dosing Instructions for Imprime PGG

Refer to Appendix 14.1 for complete instructions on the preparation and administration of Imprime PGG.

Imprime PGG is to be administered via IV infusion through a low protein binding 0.22-micrometer in-line filter; an infusion pump should be used to assure accurate and consistent dosing. Imprime PGG should not be administered as an intravenous push or bolus. Table 6 below on Target Imprime PGG Administration Values describes recommended concentration, dilution volume, and administration time. Dependent upon actual total body weight on Cycle 1/Day 1, the concentration of the final diluted solution and the rate of infusion may be outside of the values in Table 6, but should not exceed 0.8 mg/mL or 4.2 ml/min respectively. Site standard guidelines should be utilized for any re-calculations of study medication based on weight change.

Table 6. Target Imprime PGG Administration Values

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

Note: Concentration and rate calculations are based upon an average weight of 75 kg and are approximate; actual values will differ among subjects based upon total body weight and may therefore be outside of the ranges presented above in Table 6.

Please refer to Section 5.2.1.2.1 for instructions on handling infusion reactions related to the administration of Imprime PGG.

10.6 Preparation and Dosing Instructions for Pembrolizumab

Subjects will receive pembrolizumab at a dose of 200 mg IV on D1 of every 3-week cycle.

The lyophilized powder for pembrolizumab should be reconstituted and prepared per the pembrolizumab package insert (see Appendix 14.2).

Pembrolizumab should be administered on D1 of each 3-week cycle intravenously over 30 minutes.

Please refer to Section 5.2.1.2.2 for instructions on handling infusion reactions related to the administration of pembrolizumab.

Please refer to the pembrolizumab regional prescribing guidelines for complete instructions on the preparation, storage, handling, administration, and toxicity of pembrolizumab.

11.0 CLINICAL STUDY ADMINISTRATION

This research will be carried out in accordance with ICH Guidelines, GCP, and with applicable local regulatory requirements. A subject's voluntary signing of the informed consent is a required precondition to participating in the study.

The Investigator is responsible for ensuring that the clinical study is conducted in accordance with the principles above, the protocol, and other applicable requirements of the governing regulatory body.

12.0 INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Written informed consent, authorization of use, and disclosure of personal health information must be obtained from each subject (or the subject's legal representative) prior to performing any study-related procedures. Prior to signing the informed consent, the study must be thoroughly explained to the subject (or legal representative) and the subject must be given the opportunity to ask questions. Included in the explanation must be the aims and methods of the study, anticipated benefits, potential hazards, and any anticipated possible discomfort. It must be explained to the subjects that they are free not to participate in the study and that if they do decide to participate, they may elect to withdraw at anytime without prejudice to future care. Subjects will also be told of any available treatment alternatives.

Subjects will be told that competent authorities and authorized personnel may examine their records, but that their personal data will be kept strictly confidential and will not be made publicly available, nor will it be used for reasons other than those outlined in the informed consent. The subject's dated signature on the IRB/IEC-approved form constitutes consent. If a subject and/or his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion and the signature of the witness must be on the informed consent. The informed consent presented to the subject must be in his/her primary language and must have been IRB/IEC-approved.

One copy of the signed informed consent document and authorization will be given to the subject and the Investigator will retain another. The informed consent document and authorization, which is prepared by the Investigator, must have been reviewed and approved by the Sponsor, the Investigator's IRB/IEC, and privacy board, as applicable, prior to the initiation of the study. The consent document must contain the 20 elements of informed consent described in ICH E6 Section 4.8. The site shall document the informed consent process.

12.1 Study Documentation

12.1.1 Study Files

Documentation concerning Investigator data, IRB/IEC data, and clinical laboratory data, as well as the signed protocol page and a blank copy of the IRB/IEC-approved informed consent document and authorization are required before study unit initiation. Copies of these documents as well as supplemental information, such as the Investigators Brochure, Responsibilities and Obligations of Investigators and Sponsor, and final protocol, including any amendments, will be kept on-site in a special study file. This file also will contain the

Statement of Investigator Forms (or other forms required by the governing regulatory agency) and curricula vitae for the principal Investigator(s) and each Subinvestigator, subject accountability records, drug accountability (receipt/dispensing) records, Sponsor or Sponsor's representative/Investigator correspondence, IRB/IEC correspondence, changes to the protocol, information regarding monitoring activities, biological samples records, and SAE/Safety reports.

12.1.2 Case Report Forms and Source Documentation

Source documents are the records maintained at the clinical research center that represent the first written (handwritten or electronic) record of subject information. Source documents include signed informed consent forms, written progress notes, laboratory reports, ECG tracings, etc. All source documents must be maintained at the clinical research center. Handwritten source documents should be recorded in blue or black ink. Any corrections to these handwritten source documents should be made by a single line drawn through the entry, adding the correct information, initialing and dating by the person making the change, and (preferably) indicating why the change was required.

Electronic case report forms will be used for this study. The Investigator will ensure that all data are entered promptly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs, designed specifically for this study and supplied by the Sponsor or Sponsor's representative.

Data will be recorded at the investigational site and reviewed by the Sponsor (or Sponsor's representative)-assigned clinical research associate (CRA) during monitoring visits. The eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for and when each casebook has been reviewed and signed by the Investigator, indicating his/her assurance of the accuracy of all recorded data.

12.1.3 Retention of Study Documents

Regulatory agencies require retention of study records for 7 years (or longer as required by specific countries regulatory agencies) following the termination of all clinical activities with the study drug or 7 years (or longer as required by specific countries regulatory agencies) following approval of the product for marketing. Since Investigators may not be aware of the date when a product is approved or withdrawn, all study-related records, including all source documents and all case report forms must be maintained for at least 10 years (or longer if requested by the Sponsor). The Sponsor will notify the Investigator when records may be destroyed or transferred. The Investigator must notify the Sponsor if the records are to be moved to an alternate storage site.

12.2 Clinical Monitoring

An authorized CRA will visit the site prior to initiation and at periodic intervals to review the study records (including ICFs, inventory of study drug, and eCRFs), and assess compliance with the study protocol. The monitor(s) will also visit at conclusion of the study to help resolve any remaining data queries and close out all record keeping.

It is the responsibility of the Investigator to make sure all necessary source documentation and records are available to the CRA during his/her visit and to provide a suitable space for the CRA to review these documents. Additionally, the Investigator must also be available as needed during the monitoring visit. It is the CRA's responsibility to arrange the visits with the unit in advance and to notify the unit of the documentation that he/she will need during the visit. If the situation warrants, and at the request of the Sponsor, an interim monitoring visit may be made without pre-notification to the unit.

All findings resulting from monitoring visits will be documented and shared with the Investigator and Sponsor via follow-up letters and monitoring reports. As much as possible, issues/discrepancies should be resolved during the monitoring visits, but those remaining at the end of the visit will be followed through until resolution.

12.3 Confidentiality

12.3.1 Data

All information regarding the nature of the proposed investigation provided by the Sponsor or CRA to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/IEC, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

12.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects' initials and an assigned subject number (only) will appear on any document submitted to the Sponsor or Sponsor-designated clinical research organization (CRO). Documents that will not be submitted to the CRO and that identify the subject (eg, the signed ICF) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the CRA, or Sponsor representatives.

12.3.3 Publication and Use of Information

All information concerning Imprime PGG, Sponsor's patent applications, formulas, operating procedures, manufacturing processes, and scientific data supplied by the Sponsor and not previously published is considered confidential and remains the sole property of Biothera.

The Investigator agrees to use this information only to conduct this study and not to use it for other purposes without prior written consent from Biothera.

The Investigator understands information developed in the clinical study will be used by the Sponsor or its designee in connection with the continued development of Imprime PGG and thus may be disclosed to other Investigators, regulatory authorities, or groups at the Sponsor's discretion. The Investigator is obligated to provide to the Sponsor all data generated from this study.

Any publication or other public presentation of data from this study is at the sole discretion of the Sponsor and requires Sponsor review and written approval. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Please refer to the full publication guidelines at http://www.icmje.org/.

Requests for review of material for publications must be made to the Sponsor at least 30 days prior to any applicable submission deadline. Further, upon request, such submission shall be deferred for an additional period not exceeding 90 days to enable the Sponsor to protect its right in maintaining the confidentiality of proprietary information.

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14.0 APPENDICES

14.1 Imprime PGG 4 mg/kg and 2 mg/kg Preparation and Dosing Instructions

Table 14. 1. Imprime PGG Injection Preparation and Dose Levels

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

Imprime PGG Injection is supplied in 20 mL or 50 mL vials containing 20 mg or 50 mg respectively of Imprime PGG (1.0 mg/mL). Imprime PGG Injection should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution in the vial should be clear and colorless however it may contain a small amount of visible, white, amorphous particulates (precipitate). Imprime PGG is 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; an infusion pump should be used to assure accurate and consistent dosing. Do not administer Imprime PGG as an intravenous push or bolus. Table 14.1 describes total infusion volumes, administration times, and rate of infusion for the study dose. Do not exceed an infusion rate of 4.2 ml/min. 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 2-8° C.

The Imprime PGG infusion should be prepared as follows for a dose of 4 mg/kg:

1. **Determine the Imprime PGG dose/dose volume needed**
   A. Example (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 mL of Imprime PGG
   - Subject who weighs 70 kg should receive 280 mg, 280 mL of Imprime PGG prepared as described further in Steps 2 – 6 below.

   B. Example (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 mL of Imprime PGG
   - Subject who weighs 100 kg should receive 400 mg, 400 mL of Imprime PGG prepared as described further in Steps 2 – 6 below.

   C. Example (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 mL of Imprime PGG
- Subject who weighs 160 kg should receive 640 mg, 640 mL of Imprime PGG 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 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.

A. Example (For weight <75 kg):
- Since subject weighs 70 kg, a 500 mL 0.9% NS bag should be used. Withdraw and discard 280 mL of NS from the 500 mL NS bag.

B. Example (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 mL of NS from the 750 mL NS bag.

C. Example (For weight >150 kg):
- Since subject weighs 160 kg, a 1000 mL 0.9% NS bag should be used. Withdraw and discard 640 mL of NS from the 1000 mL NS bag.

3. Withdraw the calculated Imprime PGG dose volume from the Imprime PGG vials (from Step 1).

A. Example (For weight <75 kg):
- For a subject weighing 70 kg, withdraw the required 280 mg (280 mL) from the Imprime PGG vials, and inject the Imprime PGG into the NS bag and mix gently.

B. Example (For weight >75 kg, up to ≤150 kg):
- For a subject weighing 100 kg, withdraw the required 400 mg (400 mL) from the Imprime PGG vials, and inject the Imprime PGG into the NS bag and mix gently.

C. Example (For weight >150 kg):
- For a subject weighing 160 kg, withdraw the required 640 mg (640 mL) from the Imprime PGG vials, and inject the Imprime PGG into the NS bag and mix gently.

4. Label bag appropriately.

5. Attach appropriate IV tubing and using an infusion pump infuse at the rate determined by the total infusion volume/infusion time described above.

A. Example (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

B. Example (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

C. Example (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.

<u>The Imprime PGG infusion should be prepared as follows for a dose of 2 mg/kg:</u>

1. Determine the Imprime PGG dose/dose volume needed

A. Example (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.

B. Example (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.

C. 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.**

A. Example (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.

B. Example (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.

C. Example (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).

A. Example (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.

B. Example (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.

C. Example (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 i.v. tubing, and using an infusion pump infuse at the rate determined by the total infusion volume/infusion time described:

A. Example (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

B. Example (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

C. Example (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.

14.2 Pembrolizumab (KEYTRUDA®) Package Insert and Summary of Product Characteristics [Annex I of the European Public Assessment Report (EPAR)]

https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf

14.3 ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living abilities of the subject, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Source: www.ecog.org/general/perf_stat.html

14.4 Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

http://www.oncology.tv/SymptomManagement/NationalCancerInstituteUpdatesCTCAEtov403.aspx

14.5 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Criteria for Evaluating Response in Solid Tumors

http://www.eortc.be/Recist/documents/RECISTGuidelines.pdf

14.6 Immune Related Response Criteria (irRECIST)

Table 14.6 Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every 6 week (±7 days) imaging schedule

If tumor imaging shows initial disease progression, the Investigator may elect to continue treatment, repeat imaging ≥ 4 weeks later and assess tumor response or confirmed progression per irRECIST (see Section 7.3.2 and Table 14.6 above).

irRECIST is RECIST 1.1 adapted as described in the Table 14.6 to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST may be used by the Investigator to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database.

- In determining whether or not the tumor burden has increased or decreased, the Investigator should consider all target lesions as well as non-target lesions. Subjects who

are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

- For a **clinically stable** subject with first radiologic evidence of PD by RECIST 1.1 (ie, **unconfirmed progression of disease**), it is at the discretion of the Investigator to continue treating the subject per the protocol until PD is confirmed at least 28 days from the date of the scan first suggesting PD. If radiologic progression is confirmed by subsequent scan, then the subject will be discontinued from study treatment. If radiologic progression is not confirmed by irRECIST per the Investigator, then the subjects may continue on treatment and follow the regular imaging schedule intervals until PD is confirmed at a later timepoint by the Investigator.
    - **NOTE**: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.1 Schedule of Assessments - Study Flow Chart.
- Any subject deemed **clinically unstable** should be discontinued from study treatment at first radiologic evidence of PD, and is not required to have repeat imaging for PD confirmation.
- In subjects who discontinue study treatment without documented PD, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 6 weeks ± 7 days), until (1) the start of new anti-cancer treatment, (2) PD, (3) death, or (4) the end of the study, whichever occurs first.

INFORMED CONSENT

TITLE:	A Multicenter, Open-label, Phase 2 Study of Imprime PGG and Pembrolizumab in Subjects With Advanced Melanoma Failing Front-line Treatment with Checkpoint Inhibitors (CPI) or Triple Negative Breast Cancer (TNBC) Failing Front-line Chemotherapy for Metastatic Disease
PROTOCOL NO.:	BT-CL-PGG-MEL/BCA-1621/MK3475 PN-545/Amendment 001 WIRB® Protocol #20162506
SPONSOR:	Biothera Pharmaceuticals, Inc.
INVESTIGATOR:	Name Address City, State Zip Country
STUDY-RELATED PHONE NUMBER(S):	Name Phone number (24-hour number required)

Introduction

You have been asked to participate in a research study. In order to decide whether you agree to be part of this research study, you should read this informed consent, which describes how the study will be done and the possible risks and benefits.

Please take your time to make your decision about taking part. You may discuss your decision with your friends and family or your healthcare team. If you have any questions, you can ask your study doctor for more explanation.

If you agree to take part in this study, you will be asked to sign this form. You will be given a copy to keep. If you do not sign this form, you cannot take part in this study.

You are being asked to take part in this study because you have either:

- Metastatic Triple-Negative Breast Cancer (TNBC) and you have gotten worse after treatment with chemotherapy

or

- Advanced (unresectable [cannot be removed surgically] Stage III or Stage IV) melanoma and you have gotten worse after treatment with a type of medication called a “checkpoint inhibitor”

Why is this study being done?

The purpose of this study is to find out good and/or bad effects of the investigational drug, Imprime PGG, when given together with pembrolizumab which is also known as “Keytruda®” (a type of “checkpoint inhibitor”) in the treatment of your type of cancer. An investigational drug is one that is not approved by the United States Food and Drug Administration (FDA). Imprime PGG is a glucan. Glucans are molecules that are not normally present in your body. Imprime PGG when given with pembrolizumab may help the immune system to fight your type of cancer. Pembrolizumab is already approved by the FDA when given alone for the treatment of advanced metastatic melanoma, but not for TNBC. The combination of these drugs used in this study is also investigational.

Biothera is the sponsor supporting this study and is responsible for the manufacturing of Imprime PGG.

Pembrolizumab is manufactured by Merck.

The term “study drug” or “study medication” will be used throughout this document to refer to both Imprime PGG and pembrolizumab.

How many people will take part in the study?

The goal of the research study is for up to 94 people (up to 41 who have melanoma and up to 53 who have TNBC) to participate throughout the United States.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study

You will have the following exams, tests, or procedures to find out if you can be in the study - this is called the screening period. These exams, tests, or procedures may be part of your regular cancer care and may be done even if you do not join the study. If you have had some of them recently (within days before the start of the treatment on this study), they may or may not need to be repeated. This will be up to your study doctor. These screening tests and procedures include the following:

- You will be asked to sign this consent form before any screening tests can be performed.
- If you are a female who is able to have children, a urine or blood pregnancy test will be done. You will not be allowed to enter the study if you are pregnant, or if you are breast-feeding.
- You will be asked about your past and present medical history including information about you, and medications (prescription, over the counter, and herbal) you are currently taking or have recently taken and the reason that you took them.
- Your performance status will be done which is a general assessment (questions) of how your cancer is affecting your daily life, and how well you can carry out daily activities.
- A physical examination including measurement of your vital signs (heart rate, breathing rate, blood pressure), weight, and height will be done.
- Blood samples (approximately 18 mL or about 3 and a half teaspoons) and a urine sample will be collected for routine tests.
- A screening blood sample (5 ml or 1 teaspoon) will also be collected to see if certain antibodies and proteins are present in your blood prior to your participation in the research

study; if you have previously been pre-screened with this blood test, you will not need to repeat it. Additional blood samples (5 ml or 1 teaspoon) will be collected during the study to see the effects of the study drug on your body.

- An electrocardiogram (ECG) will be done to check the rhythm (tracing of the electrical activity) of your heart.
- A computed tomography (CT) scan with contrast (you will be injected with a dye prior to the procedure to make the organs and tissues that are being scanned more visible) or magnetic resonance imaging (MRI) of the head, chest, abdomen, and pelvis are required within 28 days of starting study drug. CT or MRI only needs to be performed if it hasn't been done within the required time period. If your study doctor believes your cancer has spread to your bones, you may be asked to have a bone scan. A bone scan is a diagnostic procedure used to evaluate abnormalities involving bones and joints.
- The pathology report describing your cancer upon initial diagnosis, and if available, a section of your archived cancer biopsy (which was taken from you in the past when you were first diagnosed with cancer), will be provided to the study researchers.

During the Study

Everyone in this study will get the same treatment of Imprime PGG in combination with pembrolizumab.

If the exams, tests, and procedures completed for the screening period show that you can be in the study, the study doctor feels it is safe for you to do so, and you choose to take part, you will be receiving Imprime PGG + pembrolizumab.

Treatment will occur in 3-week cycles.

Each cycle begins immediately after the end of the previous cycle so treatment continues without any gaps in the cycles for as long as you are receiving study drug.

Imprime PGG and pembrolizumab are both given through a needle in a vein as an intravenous (IV) line or through a previously surgically inserted venous access line, also known as a Port or PICC line.

You may receive medications before receiving the study medications, and these medications are called "pre-treatment". This pre-treatment is given to help your body tolerate the study medications better, and help to decrease the chance of an allergic type reaction. An anti-histamine drug (for example, Benadryl or equivalent) or other drugs which your doctor feels may help you will be given before administration of the study drug. You will then receive the Imprime PGG over a 2-4 hour period depending on your weight. After the Imprime PGG administration is completed, you will wait 15-30 minutes, (a rest period) and then receive the pembrolizumab over approximately 30 minutes.

You will need to be in the clinic for about 3 hours for each visit for all but 2 visits.

During 2 visits (Day 1 of Cycle 1 and Day 1 of Cycle 3) when extra blood samples will be drawn for a pharmacokinetic ("PK") analysis, you will need to stay in the clinic about 6 hours total. This includes your treatment time and 3 hour wait period to draw the PK blood work.

To find out how you are doing, the following tests and procedures will be done while you are on the study:

Tumor Biopsies

You will be asked if you are willing to undergo three procedures to provide the study researchers with biopsy samples of your cancer tumor. You need not agree to having these procedures done, but it will be very helpful to the study researchers in order to better understand how to help other people with your same disease. Even if you agree at the start of the study to undergo these procedures, you are free to change your mind for any reason and decline, without any negative consequences to you from your doctor or any of the research staff.

If any written documents or reports about the sample are also sent with your biopsy sample(s), your name and medical records number will be removed from them.

The biopsies will be collected at the following timepoints:

1. Before Beginning Day 1 of Week 1 (First Cycle)
2. After Finishing Cycle 2 But Before Beginning Day 1 of Cycle 3
3. At Time of Response or End of Study Visit (just one of these times)

☐ I agree to these optional biopsies

☐ I do not agree to these optional biopsies

Day 1 (All Cycles)

- A general assessment performance status (questions) of how your cancer is affecting your daily life and how well you can carry out daily activities will be done**.**
- Your weight (which is important to determine your correct dose of study medication) will be measured.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are new or different for you than you normally feel) and any new medications or changes to medications you have taken.
- Blood samples will be collected for both routine tests and study-specific tests, unless these tests were performed less than 3 days prior to Day 1. The results of your blood tests will be reviewed by the study doctor prior to study drug administration. Therefore, this may require a separate visit each week for the blood draw prior to your treatment day, which can be scheduled up to 3 days prior to your treatment day, in order to allow for testing and processing of the blood sample.
- The maximum amount of blood taken on any one day will be on the first day of the study when 84 mL (or about 17 teaspoons) will be collected (this includes PK samples listed below). On all other first days of subsequent cycles, the amount will vary from 3 mL (a little over half a teaspoon) to 54 mL (about 11 teaspoons). The site staff have been given a chart showing exactly how much blood will be collected for which tests at every visit.

- Part of the blood sample collected will include 20 mL (about 4 teaspoons) to see if certain antibodies and proteins are present in your blood and to see the effects of the study drug on your body.
- You will receive Imprime PGG first and then pembrolizumab.

Day 8 and Day 15 (All Cycles)

- You will receive an infusion of Imprime PGG.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are different from you normally feel) and any new medications or changes to medications you have taken.

Cycle 1 and Cycle 3 Only (Week 1 and Week 7)

- Blood samples will be collected for pharmacokinetic (PK) testing. PK testing measures the amount of study drug that is circulating in the blood. You will spend additional time in the clinic for the study staff to collect the blood samples after the study drug administration. A total of 4 blood samples will be drawn, with the last one being about 6 hours after you start getting your first study drug infusion. A total of 20 mL (about 4 teaspoons) will be taken for this PK testing.

Every Other Cycle (Every 6 Weeks)

- In addition to the blood samples discussed earlier, a CT scan with contrast, or MRI scan of the head, chest, abdomen and pelvis, will be done. If necessary, a bone scan will be done.

These tests and procedures may be part of regular cancer care. However, these tests and procedures may be done more often because you are in this study or because your study doctor feels it is necessary.

End of Treatment Visit

Within 3 days after the end of the cycle in which you received your last dose of study medication, the following tests and procedures will be performed:

- A general assessment performance status (questions) of how your cancer is affecting your daily life and how well you can carry out daily activities will be done**.**
- A physical examination will be done and your weight will be measured.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are new or different for you than you normally feel) and any new medications or changes to medications you have taken.
- A voluntary procedure to provide the study researchers with a biopsy sample of your cancer tumor, as discussed in detail earlier.
- Blood samples for routine tests and study-specific test totaling about 39 mL (about 8 teaspoons).

Post-Treatment Visit

Approximately 4 weeks after your last dose of study medication, the following tests and procedures will be performed:

- If you are a female who can have children, a urine or blood pregnancy test will be done.
- A general assessment performance status (questions) of how your cancer is affecting your daily life and how well you can carry out daily activities will be done.
- You will be asked about your health, and any adverse events (any symptoms good or bad that you felt during the week after you received the study medications that are new or different for you than you normally feel) and any new medications or changes to medications you have taken.
- Blood samples for routine tests and study-specific test totaling 23 mL (a little over 4.5 teaspoons).

Follow-up After Completion of the Post-treatment Visit

The study staff will call you every 2 months after your last study visit in the office to ask about any further treatment you may have received or are currently receiving for your cancer. You may be asked to have a CT with contrast or MRI scans every 6 weeks to monitor your cancer. This follow-up will end once the whole study finishes for everyone, which is expected to be approximately 3 years after the last patient who enrolled in this study took his/her first dose of study medication.

How long will I be in the study?

You will receive Imprime PGG + pembrolizumab in 3-week cycles. The 3-week cycles will continue until you have received treatment in the study for 2 years, until your cancer shows signs of progression, or you experience unacceptable toxicities, whichever occurs first.

Sometimes with checkpoint inhibitors such as pembrolizumab, your cancer may temporarily get worse (or show signs of progression) because the drug is helping your body to fight the cancer cells. This is sometimes called an “immune response”. If your doctor thinks this is happening to you, he/she will discuss with you the option to stay on the same study treatment you are on and check the size and number of your tumor(s) within about 4 weeks by taking an additional MRI or CT scan. During this time, your doctor will monitor your health carefully.

If this does happen, your doctor will review your treatment options with you before continuing study treatment, and will explain your treatment plan. If you decide to remain in the study, you will sign below, which means you understand your doctor thinks the study medications are helping you to fight your cancer, even though it looks like your cancer is getting worse. You agree to allow your doctor to continue treating you with the same study medications until your doctor knows the results of the additional MRI or CT scan. Your doctor will then review your results with you and if your cancer is improving, you will remain on the study. But if your cancer stays the same or has become even worse, your participation in the study will end.

Statement of Professional Obtaining Consent

I have fully explained what may be happening with the research participant's response to the study medications. In my judgment, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____

Signature of Person Obtaining Consent: _____

Printed Name of Person Obtaining Consent: _____

After the last study visit in the office, study staff will call you every 2 months up until 3 years have passed since the last patient's first dose of study medication, and the study staff will ask about any additional cancer treatment you have received.

If you stop receiving study medication because you have achieved a Complete Response, and then your cancer recurs, you may be able to go back onto the study medication as long as the study is still ongoing.

It is possible that your study doctor or the sponsor will decide to end your participation in the study without your consent for any reason. Reasons for doing so include the following:

- If your study doctor does not think it is best for you to continue
- If your condition gets worse
- If you have serious side effects
- If you develop a serious illness, even if it is not related to your taking part in the study
- New information becomes available that shows this study in not the best option for you
- If you become pregnant, or you are nursing during this study
- If the entire study is discontinued
- If you are unable or are unwilling to follow the instructions for taking part in the study
- If you no longer meet the requirements for the study

Biothera, the FDA, an Institutional Review Board (IRB), an Ethics Committee, or other regulatory agencies may decide to stop the study before the study is done and without warning. If this happens to you, your study doctor will assist you with the plans for your continued care as appropriate.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched for side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Side effects may go away soon after you stop taking Imprime PGG and/or pembrolizumab. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.

As with any new substance like Imprime PGG, new, previously unknown side effects may also occur.

This section uses symbols to describe the frequency of side effect occurrences. The following is included as a key to help you understand these symbols:

Symbol	Meaning
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Imprime PGG

Common side effects seen in > 5% of patients treated with Imprime PGG in the healthy volunteer studies of Imprime PGG, when it was given as a single agent without premedication include the following:

- Shortness of breath
- headache
- tingling sensations
- rash
- nausea
- flushing (reddening of the face)
- red eyes
- blurred vision
- fatigue
- low red blood cell count
- dizziness
- numbness
- bruising
- sweating
- itching
- sore throat
- chest discomfort
- chills
- pain at injection site
- incidental back injury
- laceration or scratch
- fast heart-beat
- upper respiratory infection
- low white blood cell count
- joint aches or stiffness

Common side effects seen in more than 5% of subjects who received Imprime PGG in the healthy volunteer studies of Imprime PGG, when it was given in combination with filgrastim (Neupogen®):

- Abdominal (stomach) pain
- nausea
- chest discomfort
- chest pain
- chills
- injection site irritation
- injection site pain
- pain
- joint aches
- back pain
- musculoskeletal (muscles and bones in the body) pain
- pain in arms or legs
- dizziness
- headache
- shortness of breath
- rash
- hives

There were a few severe side effects which included:

- stomach pain
- hypersensitivity
- low blood pressure
- rapid heartbeat
- injection site pain and injection site swelling

Imprime PGG has been studied in patients with advanced cancer. The patients in these studies were also taking several other medications (eg antibodies, chemotherapy) to treat the cancer, in combination with Imprime PGG. The side effects seen in these studies have been similar to the side effects expected to be seen in patients that take these other medications (eg antibodies, chemotherapy).

In previous studies with another drug substance (Betafectin®) that contained the same active ingredient (PGG Beta Glucan) as Imprime PGG, other observed side effects included inflammation of the joints and eyes, permanent liver damage, fever, and dilation of blood vessels were observed. The side effects of Imprime PGG may be similar to those seen with Betafectin®.

Pembrolizumab

What is known about this study drug?

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer.

Pembrolizumab works by helping your immune system to fight your cancer.

However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or life-threatening, and in some cases, may lead to death.

What side effects could the study drug cause?

VERY COMMON. SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and /or feel sick to your stomach

UNCOMMON, SOME MAY BE SERIOUS (i.e. cause hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death.

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in the muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing

- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

In addition to the above, **if you have had** an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, **after receiving pembrolizumab**. Sometimes this condition can lead to death.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide (drugs related to thalidomide which affect the body's immune system) and dexamethasone (a steroid) had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide.

To date, there have been no studies conducted using a combination of Imprime PGG and pembrolizumab. Therefore, it is not known what types of side effects might be observed or which you might experience with this combination.

Due to the unknown effects of the study medication, you should be aware that the consumption of alcohol or the taking of any drugs or medication (with or without prescription or illegal ones), other than the study medications, at any time during the study without the consent of the study doctor or site staff might cause serious or even life-threatening reactions. Both new and current drugs can have unknown side effects, some of which might be serious.

0.9% Normal Saline (Sodium Chloride):

Infusion of normal saline can result in infusion site swelling, tenderness, redness, or infiltration (normal saline leaking into the tissue around the vein). More serious side effects may include increased heart rate, fever, rash, joint pain or shortness of breath.

Diphenhydramine (Antihistamine):

Diphenhydramine is used to treat symptoms of allergies such as runny nose, sneezing and itchy eyes, nose or throat. It is also used as a sleep aid or to decrease motion sickness. More common side effects include drowsiness, dry mouth (nose and throat), dizziness, nausea, headache, tightening of the chest and loss of appetite. More serious side effects may include change in vision, decrease or trouble urinating or trouble breathing.

Infusion Site Reaction:

It is possible to have what is called an infusion site reaction following an intravenous (IV) infusion (medication given through a needle in a vein). Symptoms of an infusion site reaction may include, pain, redness, burning sensation, and itching sensation. You may experience inflammation or infection at the infusion site. If you experience any of these report it to the clinic staff. The infusion site will be monitored throughout the study.

Allergic Reaction:

It is possible to have what is called an allergic (or hypersensitivity) reaction during or soon after the administration of any investigational or non-investigational medicine. Some subjects have experienced difficulty breathing, wheezing, hives or swelling around the vein where the needle was placed, face, mouth, lips, gums, tongue, or neck. If you have any allergies that you are aware of, you should tell the study doctor before agreeing to take part in this study. Since Imprime PGG is investigational when taken alone or in combination with other medications, there may be other risks that are unknown.

All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening. If you experience any such symptoms, you should get medical help and contact the study doctor right away.

Risks and possible discomforts you might experience from the study procedures include:

Blood draws: Temporary discomfort from the needle in your arm, bruising, bleeding, and swelling at the needle insertion site or vein [phlebitis], and infection. Standard medical care will be taken to avoid these complications.

ECG: The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches.

CT Scan Risks: In this study, you will be exposed to some radiation from the CT scans. The amount of radiation you will get is like the amount from other x-ray exams routinely used in medicine. Public policy is to keep exposure levels as low as possible.

Contrast dye may be used, which has a small possibility of a severe allergic reaction and kidney problems.

MRI Scan risk: You may have risks from MRI if you have metallic objects in your body. You may also become anxious from lying in a tight space without moving.

Other Risks:

Since Imprime PGG is investigational, there may be other risks that are unknown. For your own safety and for the safety of other subjects in the study, you must inform the study doctor or study staff about any side effects or other health problems you experience during the study. Other medicines or supplements could cause side effects if you use them while you are receiving Imprime PGG. Because of this, you must tell the study doctor or a member of the study staff about all of your past and present illnesses and allergies. You must also tell them about all drugs, vitamins, supplements, and medicines you are taking.

It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are on the first page of this document.

REPRODUCTION RISKS

Pregnancy Related Risks / Use of Birth Control Females

The effects of Imprime PGG on pregnancy, an unborn baby, or a nursing child are not known. If you are currently pregnant, planning to become pregnant, or are breastfeeding a child, you should not take part in this study.

All females who are able to get pregnant and males whose partners are able to get pregnant and who are sexually active are required to use an acceptable form of contraception (birth control) during the study and continue contraception for 120 days after the last dose of study drug. Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% when used consistently and correctly. The study doctor will instruct you in correct use of your selected birth control method and review with you at each visit your responsibility to use your selected birth control method consistently and correctly.

The following are highly effective methods of acceptable birth control:

- Abstinence (refraining from intercourse for the required study period)
- Correctly placed copper containing intrauterine device (IUD).
- Contraceptive rod implanted into the skin
- Male sterilization of subject or female subjects' partner with confirmed absence of sperm in the post-vasectomy ejaculate.
- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Use of 2 of the following:

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide
- Contraceptive sponge
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill, contraceptive skin patch, vaginal contraceptive ring, or subcutaneous (under the skin) contraceptive injection

Discuss any other forms of birth control with your study doctor to see if they are acceptable.

Birth control methods, even when used consistently and correctly, are not perfect. If you become pregnant or want to stop your required birth control while you are in the study, you should tell the study doctor immediately. You will be withdrawn from the study if you discontinue birth control or you become pregnant.

Males

The effects of Imprime PGG on sperm or a pregnancy are not known. If you are planning to father a child you should not join this study. If you and your partner are physically able to have children and you are sexually active, you must use an acceptable form of the birth control from the methods listed above consistently and correctly beginning with the first infusion of the study drug and at least 120 days after the last injection of the study drug. The study doctor will discuss

with you the permitted methods of birth control for this study and will help you select birth control that is appropriate for you. The study doctor will instruct you in correct use of your selected birth control method and review with you at each visit your responsibility to use your selected birth control method consistently and correctly.

Pregnancy Follow Up

If you become pregnant during the study or within at least 120 days, after the last infusion of the study drug, please tell the study doctor immediately. Please also tell the doctor who will be taking care of you during the pregnancy that you took part in this study. The study doctor will ask if you or your pregnancy doctor are willing to provide updates on the progress of the pregnancy and its outcome. If you agree, this information will be provided to the study sponsor for safety monitoring follow-up.

What if New Information Becomes Available?

The study doctor will tell you in a timely manner of any information learned during the course of the study that might cause you to change your mind about taking part in the study. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

As with any new substance, new and/or previously unknown side effects may also occur with the use of Imprime PGG.

Are there benefits to taking part in the study?

Taking part in this study may or may not help your cancer. The information learned from this study may help doctors learn more about the combination of Imprime PGG and pembrolizumab as a treatment for people with cancer such as yours. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer with a different cancer drug without being in a study
    - If you have advanced melanoma, the following is a list of other medication options available to you (in alphabetical order):
        - Aldesleukin for metastatic melanoma
        - Cobimetinib in combination with vemurafenib for BRAF-mutated unresectable or metastatic melanoma (BRAF is a protein which is involved in sending signals in cells and cell growth, and a mutation in BRAF can increase the growth and spread of cancer cells)
        - Dabrafenib for BRAF-mutated unresectable or metastatic melanoma
        - Dacarbazine for metastatic melanoma
        - Ipilimumab for adjuvant treatment after surgical removal of melanoma at high risk of recurrence OR for unresectable or metastatic melanoma

    - Nivolumab used with Ipilimumab for BRAF-unmutated unresectable or metastatic melanoma OR alone in refractory melanoma after treatment with Ipilimumab or BRAF inhibitor if BRAF-mutated tumor
    - Peginterferon Alfa-2b for melanoma spread to lymph nodes after surgical removal of skin melanoma
    - Pembrolizumab for unresectable or metastatic melanoma (if you decide to participate in this study, you will receive pembrolizumab + Imprime PGG)
    - Talimogene Laherparepvec for local injection into recurrent melanoma of the skin or lymph nodes that are unresectable
    - Trametinib for BRAF-mutated unresectable or metastatic melanoma
    - Vemurafenib for BRAF-mutated unresectable or metastatic melanoma
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about all of your choices before you decide if you will take part in this study. There may be new treatments your doctor can tell you about, which were not yet approved at the time this Informed Consent Form was written.

What are my responsibilities if I decide to participate?

If you decide that you want to participate in the study, you will be asked to come to all of your scheduled study visits, to follow the study doctor's directions, and to inform the study staff about any new medications you are taking and how you have been feeling.

Will my medical information be kept private?

Every effort will be made to keep your study records private. It is the responsibility of the study staff to make sure that your research records are protected. If information from this study is used in any reports or publications, your name and anything else that could identify you will not be used. The study staff will review your records and require access to your medical information.

Other organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government regulatory agencies like the US Food and Drug Administration (FDA)
- Biothera the study sponsor, Merck (manufacturer of pembrolizumab), and representatives working on behalf of the sponsor
- Regulatory agencies in other countries
- Western Institutional Review Board® (WIRB®)

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

What are the costs of taking part in this study?

The sponsor will provide Imprime PGG and pembrolizumab at no cost to you or your health insurance. You and/or your health plan/insurance company will be charged for the costs of treating your cancer including the costs of the:

- Imaging scans
- Doctor visits
- Regular tests of blood to test your health

You/your insurance will NOT be charged for the following:

- Blood tests for research purposes only
- ECGs required for research purposes only
- Tests on your tumor for research purposes only

Some health plans will not pay the costs for taking part in studies. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Check with your health plan or insurance company to find out what they will pay for.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

If, during the study, Imprime PGG becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your doctor if you feel that you have been injured because of taking part in this study. They will treat you or refer you for treatment. If, during the course of the study, you experience any injury as a direct result of the administration of study drug, the sponsor agrees to pay all medical expenses necessary to treat such injury (1) to the extent you are not otherwise reimbursed by medical insurance, a government program, or a third party, and (2) provided you have followed the directions of the study doctor.

You will not be financially compensated for your participation in this trial beyond what may be provided for time and travel. Payment for such things as lost wages, expenses other than medical care, or pain and suffering is not available.

To help avoid injury, it is very important to follow all study directions. By signing and dating this form, you have not waived any of the legal rights to pursue a claim through the legal system, which you would have otherwise, if you were not a participant in a drug research study.

Is my participation voluntary?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, complaints, or concerns you have about this study or if at any time you feel you have had a research-related injury or reaction to the study drugs.

If you have any questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, please contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

About Using Tissue and Blood Specimens for Research

You have had a biopsy (or surgery) of your cancer tumor(s) in the past to see if you have cancer. Your doctor removed some body tissue to do some pathology tests (tests and examination of your cancer tissue under a microscope). The results of these tests (the pathology report) confirmed that you have cancer. You will need to provide permission for this pathology tissue to be further examined for use this study.

You will need to provide permission for your pathology tissue sample to be sent to a central testing facility for this study. It may be tested for biomarkers (a substance that can be measured which is indicative of your disease). Additional biomarkers may be evaluated as new information becomes available from research studies. These results will become part of the study record. All possible measures will be used to protect your privacy and confidentiality, such as the use of a study number specific to you in place of your name on the results. Any unused tumor tissue samples will be returned to your study doctor 6 months after the study has ended, or sooner should you request them earlier. There will also be 3 additional tumor biopsy samples that we would like to collect. You will need to provide permission for these samples to be collected.

As described earlier, an additional blood sample (20 mL or approximately 1.5 tablespoons) will also be collected at the timepoints specified previously in this document. The blood will be tested for markers that may be associated with side effects or response to therapy, and to learn more about the immune system and cancer.

Statement of Professional Obtaining Consent

I have fully explained this research study to the research participant. In my judgment, there was sufficient access to information, including risks and benefits to make an informed decision.

Date: _____

Signature of Person Obtaining Consent: _____

Printed Name of Person Obtaining Consent: _____

Research Participant Statement

I have read this Informed Consent. I have had the opportunity to discuss this study with my family or any trusted friends, as I desired. I have had the opportunity to discuss this study with the consenting professional and all my questions have been answered to my satisfaction. I understand that my participation is voluntary. I understand the purpose, risks, and benefits of the research study. I agree to take part in this study.

Date: _____

Patient Signature: _____

Patient Printed Name: _____

The following section is only to be used after a discussion about continuing on treatment after possible pseudo-disease progression.

Research Participant Statement to Continue Research Participation

I have read the section of the Informed Consent about why my cancer may be improving even though the results look worse. I have had the opportunity to discuss this result with my family or any trusted friends, as I desired. I have had the opportunity to discuss this situation with the consenting professional and all my questions have been answered to my satisfaction. I understand that my participation is voluntary. I understand the purpose, risks, and benefits of continuing in this research study. I agree to continue taking part in this study.

Date: _____

Patient Signature: _____

Patient Printed Name: _____