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TITLE:

Phase II Trial of Pembrolizumab (MK-3475) in Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-199)

IND NUMBER: 122753

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	30-MAR-2016	
Amendment 01	30-AUG-2016	Updated Exclusion criteria for pneumonitis
Amendment 02	23-FEB-2017	Increase enrollment for Cohorts 1 & 2
Amendment 03	07-JUN-2017	Added Cohorts 4 & 5
Amendment 04	20-JUL-2017	Removed PK/PD blood collection and testing
Amendment 05	08-DEC-2017	Changed Exploratory Objectives, updated dose modification guidelines and SFU language
Amendment 06	28-OCT-2019	Added liquid formulation to product description
Amendment 07	12-AUG-2021	Added language to state that upon trial completion, subjects are discontinued and may be enrolled in a pembrolizumab extension study, if available.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.10	Beginning and End of the Trial	Added language to state that upon trial completion, subjects are discontinued and may be enrolled in a pembrolizumab extension study, if available.	Subjects may be enrolled in a pembrolizumab extension study.
7.1.1.7	Assignment of Treatment/Randomization Number	Added text to state that at the end of the study and upon enrollment in an extension study, the participant will receive a new treatment/randomization number.	Subjects may be rerandomized into a pembrolizumab extension study.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.2	Subject Inclusion Criteria	Contraceptive language was updated	Revision to align with current requirements
5.1.3	Subject Exclusion Criteria	Added language regarding COVID-19 vaccines	Addition to clarify that any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed
5.5.2	Prohibited Concomitant Medications		
5.7.2	Contraception	Section removed	Revision to remove redundancy
12.8	Contraceptive Guidance	Added new section	Addition to include the definition of WOCBP

1.0 TRIAL SUMMARY

Abbreviated Title	Phase II Trial of MK-3475 in Subjects with mCRPC
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	Phase II
Clinical Indication	Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W)
Number of trial subjects	Approximately 370 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 42 days, eligible subjects will be enrolled into one of 5 cohorts based on treatment history, programmed cell death-ligand 1 (PD-L1) status (for only Cohorts 1 and 2), and RECIST 1.1 measurability. Subjects with mCRPC previously treated with docetaxel-based chemotherapy in cohorts 1 to 3 will receive monotherapy with pembrolizumab. Chemotherapy-naïve subjects with mCRPC either having failed or showing early signs of failing on enzalutamide treatment as defined by PCWG3 guidelines (eg, signs of clinical progression, increased alkaline phosphatase, prostate-specific antigen [PSA] increase, or positive imaging assessments) in Cohorts 4 and 5 will receive pembrolizumab monotherapy with their current, stable standard of care regimen of enzalutamide. In all cohorts, pembrolizumab administration will occur on Day 1 of each 3-week dosing cycle and will continue for a maximum of 35 cycles (approximately 2 years) unless specific withdrawal/discontinuation criteria are met. Treatment with pembrolizumab in all cohorts will continue until documented confirmed disease progression, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, Investigator's decision to discontinue the subject, subject discontinuation from the study, noncompliance with trial treatment or procedure requirements, subject receives 35 administrations of pembrolizumab (approximately 2 years), or administrative reasons requiring the cessation of treatment.

	Subjects who discontinue after 35 infusions of pembrolizumab for reasons other than disease progression or intolerability, or who discontinue after attaining a complete response (and had at least 8 administrations of pembrolizumab and at least 2 treatments beyond initial CR) may be eligible for up to 17 additional infusions (approximately one year) after they have experienced radiographic disease progression. After the end of treatment, each subject will be followed for the occurrence of adverse events as described under section 7.2 of the protocol. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression is confirmed by the site, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a nonrandomized, multinational, open-label trial of pembrolizumab (MK-3475) in subjects with metastatic castration-resistant prostate cancer (mCRPC). The trial will be conducted in conformance with Good Clinical Practices.

Approximately 370 subjects will be enrolled into one of 5 cohorts based on treatment history, programmed cell death-ligand 1 (PD-L1) status for Cohorts 1 and 2 only, and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 measurability. PD-L1 status and RECIST 1.1 measurability (subjects with visceral disease) will be centrally confirmed for all cohorts. All enrolled subjects will receive pembrolizumab 200 mg every 3 weeks (Q3W).

For subjects with mCRPC previously treated with docetaxel-based chemotherapy, the enrollment cohorts will be:

(Cohort 1) subjects with PD-L1 positive, RECIST 1.1-measurable disease

(Cohort 2) subjects with PD-L1 negative, RECIST 1.1-measurable disease

(Combined Cohorts 1 and 2, n≈200)

(Cohort 3) subjects with bone-metastases, RECIST 1.1 non-measurable (n≈50)

For chemotherapy-naïve subjects with mCRPC either having failed or showing early signs of failing on enzalutamide treatment as defined by PCWG3 guidelines (eg, signs of clinical progression, increased alkaline phosphatase, prostate-specific antigen [PSA] increase, or positive imaging assessments) the enrollment cohorts will be:

(Cohort 4) subjects with RECIST 1.1-measurable disease (n≈80).

(Cohort 5) subjects with bone metastases only or bone-predominant disease, RECIST 1.1 non-measurable (n≈40).

Subjects in Cohorts 4 and 5 will receive pembrolizumab monotherapy with their current, stable standard of care (SOC) regimen of enzalutamide. *Note: subjects in Cohorts 4 and 5 may have received abiraterone prior to enzalutamide.*

Bone metastases must be radiographically evident by whole body bone scintigraphy.

Participation in this trial will be dependent upon subjects supplying tumor tissue for PD-L1 biomarker analysis from a site not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization; other exceptions may be considered after Sponsor consultation). Adequacy of these specimens for PD-L1 biomarker analysis will be required by a central laboratory prior to enrollment for Cohorts 1 to 3. Subjects with visceral/measurable lesions must provide a newly obtained biopsy or a specimen obtained ≤12 months prior to the screening date, and an archival specimen, if available. Candidates for enrollment in Cohorts 1, 2, or 4 who undergo a study-related biopsy but the tissue sample is determined to be inadequate will be allowed into the study if they have provided an adequate archival specimen. Subjects in Cohort 3 or 5 must at least provide an archival specimen. Please refer to Section 7.1.2.7 for tissue sample collection requirements by cohort.

Cohorts 1 and 2 will begin enrolling irrespective of PD-L1 expression status; however, PD-L1 expression status will be monitored. Combined enrollment in Cohorts 1 and 2 will be approximately 200 subjects and approximately 60 subjects in cohort 3. Subjects will be enrolled into Cohorts 3, 4, and 5 irrespective of PD-L1 status.

All subjects will undergo radiologic imaging assessments to evaluate response to treatment at regular intervals. On study imaging will be assessed approximately every 9 weeks for one year and approximately every 12 weeks thereafter. RECIST 1.1 will be adapted per the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) as described in Section 7.1.2.6 to account for the tumor response and progression patterns seen in bone metastases in prostate cancer.

Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (See Appendix 12.6). Treatment with pembrolizumab will continue until documented confirmed disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, Investigator's decision to discontinue the subject, subject discontinuation from the study, noncompliance with trial treatment or procedure requirements, subject receives 35 administrations of pembrolizumab (approximately 2 years), or administrative reasons requiring the cessation of treatment.

Subjects who attain an Investigator-determined confirmed complete response (CR) may receive up to 35 infusions of pembrolizumab. Subjects who discontinue after 35 infusions for reasons other than disease progression or intolerability, or who discontinue after attaining a CR (and had at least 8 administrations of pembrolizumab and at least 2 treatments beyond initial CR) may be eligible for up to 17 additional infusions (approximately 1 year) of

pembrolizumab after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the Investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open (refer to Section 7.1.5.2. for further details).

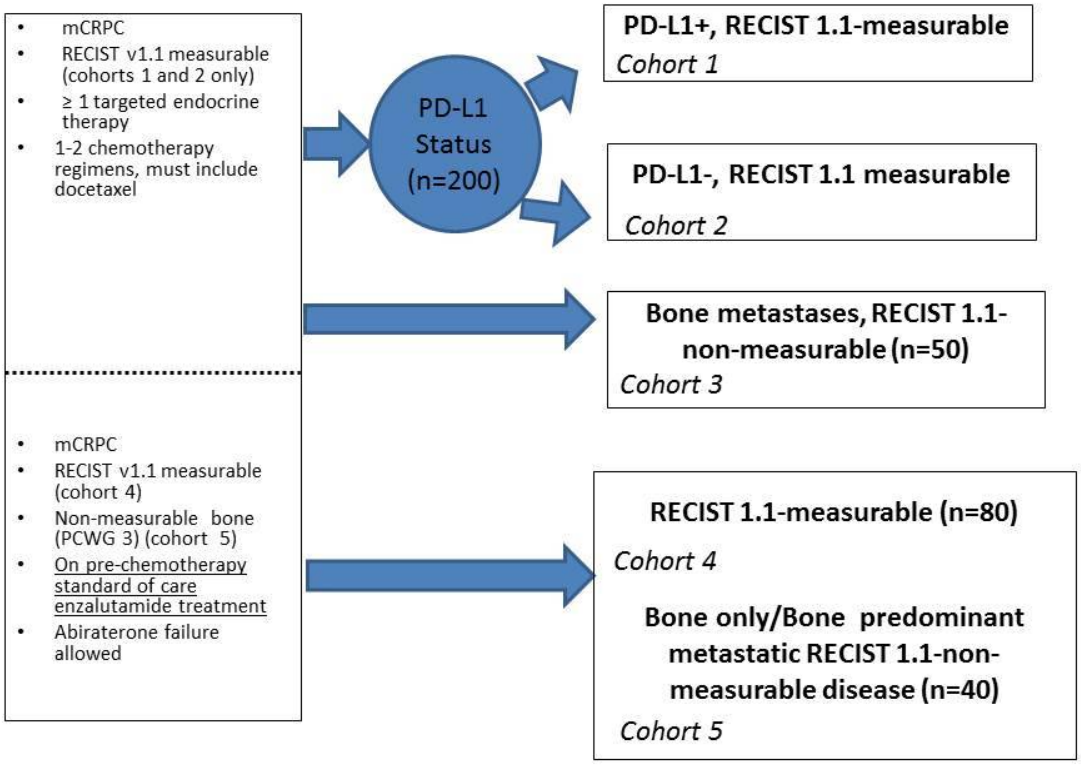
After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious AEs [SAEs] will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who discontinue treatment for reasons other than disease progression will stay on study and continue to undergo study-related disease assessments until disease progression, initiation of a non-study cancer treatment, withdrawal of consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival (OS) until death, withdrawal of consent or the end of the study, whichever comes first.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

Subjects with mCRPC with prior docetaxel and targeted endocrine therapy will concurrently enroll in Cohorts 1, 2, and 3. Chemotherapy-naïve subjects with mCRPC either having failed or showing early signs of failing on enzalutamide treatment will enroll in Cohorts 4 and 5. The trial design is depicted in Figure 1.

Figure 1 Clinical Trial Design and Enrollment Plan



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

This study has been designed to further evaluate the signal of activity observed in KEYNOTE-028 (KN028) with pembrolizumab monotherapy (see Section 4.1.3) in male subjects at least 18 years of age with mCRPC. Objectives will be assessed by enrollment cohort unless otherwise specified. There will be no hypothesis testing performed in this study.

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To estimate the objective response rate (ORR) by RECIST 1.1 in subjects with measurable disease assessed by central imaging vendor in Cohorts 1 and 2 combined, Cohort 1, Cohort 2, and Cohort 4.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To determine the safety and tolerability of pembrolizumab for all cohorts combined (Cohorts 1, 2, 3, 4, and 5) and by each cohort.

2) **Objective**: To estimate disease control rate (DCR) and radiographic progression-free survival (rPFS) by PCWG3-modified RECIST 1.1 assessed by central imaging

vendor and PSA response rate, time to PSA progression, and OS for Cohorts 1 and 2 combined, Cohorts 1, 2, and 3 combined, Cohorts 4 and 5 combined, and by each cohort.

3) **Objective:** To estimate the duration of response (DOR) by PCWG3-modified RECIST 1.1 in subjects with measurable disease assessed by central imaging vendor in Cohorts 1 and 2 combined, Cohort 1, Cohort 2, and Cohort 4.

4) **Objective:** To estimate the duration of response (DOR) by RECIST 1.1 in subjects with measurable disease assessed by central imaging vendor in Cohorts 1 and 2 combined, Cohort 1, Cohort 2, and Cohort 4.

5) **Objective**: To estimate duration of PSA response, time to initiation of cytotoxic chemotherapy, time to new-anticancer therapy, and time to first skeletal-related event in Cohorts 4 and 5.

3.3 Exploratory Objectives

1) **Objective:** To evaluate pharmacokinetic (PK) parameters and the presence of anti-drug antibodies (ADAs).

2) **Objective:** To evaluate changes in health-related quality of life assessment from baseline using FACT-P and to characterize utilities using EuroQoL-5D.

3) **Objective**: To identify molecular (including genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity and/or the mechanism of action of pembrolizumab and other treatments.

4) **Objective**: To evaluate ORR by immune-related RECIST 1.1 (irRECIST), and DCR by PCWG3-modified irRECIST assessed by central imaging vendor.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (previously known as MK-3475 and SCH 9000475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between the programmed cell death-1 (PD-1) receptor and its ligands, PD-L1 and PD-L2, without antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab is approved in the US for the treatment of patients with unresectable or metastatic melanoma (MEL) and

disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an 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) [12, 13, 14, 15]. The structure of murine PD-1 has been resolved [16]. 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 CD3ζ, PKCθ, and ZAP70 which are involved in the CD3 T-cell signaling cascade [13, 17, 18, 19, 20]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [17, 21]. 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 [22, 23]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [22, 24]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [13, 15, 17]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain 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-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. 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 [13, 15, 17]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [25]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon-γ (IFN- γ), granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [15, 18, 26, 27, 28]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the IB).

In a Phase 1/2 study of 135 subjects with advanced MEL, treatment with pembrolizumab produced an ORR of 38% (95% CI, 25% to 44%). Many of the responses were durable, with a median duration that had not been reached after a median follow-up time of 11 months [29].

4.1.3 Ongoing Clinical Trials

Subjects with PD-L1 positive mCRPC have been treated with pembrolizumab monotherapy in KN028. As of 24-Jul-2015, 16 subjects with PD-L1 positive mCRPC were enrolled and treated with pembrolizumab monotherapy. All had treatment with prior docetaxel and targeted endocrine therapy. Three confirmed partial responses (PR) were reported for an ORR at that time of 19%. The responses were durable and treatment was well tolerated. This study, KEYNOTE-199 (KN199), has been designed to further evaluate the signal of activity seen in KN028 with pembrolizumab monotherapy.

Ongoing clinical trials are also being conducted in advanced MEL, non-small cell lung cancer (NSCLC), head and neck cancer, urothelial cancer, triple negative breast cancer (TNBC), gastric cancer and hematologic malignancies. For study details please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Prostate cancer represents the second most common malignancy diagnosed in men worldwide where the annual incidence has been estimated to be over 1 million and over 300,000 deaths are expected annually [30]. In the US, approximately 1 in every 6 men will be diagnosed with prostate cancer in his lifetime [31].

While many men are diagnosed with locally confined disease and may be treated definitively with radiation or surgery, men who go on to develop or are diagnosed with metastatic prostate cancer, an incurable entity, are typically treated first with androgen deprivation therapy (ADT), usually with a GnRH agonist or antagonist that results in suppression of

testosterone production in the testes. This alone often succeeds in controlling disease for some time, years in many cases. However, prostate cancer progresses invariably and requires additional systemic therapies to reestablish control of disease. The point at which prostate cancer progresses in spite of ADT alone is referred to as castrate resistance, and the disease at this point is known as (metastatic) castrate-resistant prostate cancer (mCRPC).

A number of important systemic therapies have been developed to treat mCRPC and have received regulatory approval and now comprise the current therapeutic landscape. Docetaxel became the first systemic therapy to improve survival for men with mCRPC in a randomized study with docetaxel demonstrating superior survival of median 18.9 months versus 16.5 for mitoxantrone [32]. Cabazitaxel, a second taxane, was studied versus mitoxantrone in patients after docetaxel, and it too was found to be associated with superior survival – median 15.1 months versus 12.7 with mitoxantrone [33]. Finally, the targeted endocrine therapies enzalutamide and abiraterone were examined in randomized clinical trials in patients with mCRPC before treatment with chemotherapy and found to have superior OS versus control therapy (placebo and prednisone, respectively) [34, 35].

Cabazitaxel can be a toxic therapy. Deaths occurred on study due to treatment-related neutropenia, and mortality has been reported due to treatment-related diarrhea. Its label contains a black box warning regarding risks from neutropenia and severe hypersensitivity, and other label warnings and precautions pertain to diarrhea, renal failure, prohibitive risk in elderly patients ≥ 65, and hepatic impairment. Consequently, cabazitaxel is not well utilized and consensus guidelines, such as NCCN, recommend that men with mCRPC after docetaxel should be encouraged to participate in clinical trials. Thus, an unmet medical need remains for patients after treatment in the mCRPC setting with targeted endocrine therapy and docetaxel.

KN199 is a nonrandomized, open-label, multinational trial of pembrolizumab (MK-3475) in subjects with mCRPC who are chemotherapy-naïve or have previously been treated with chemotherapy and has been designed to further evaluate the signal of activity observed in KN028.

Participation in this trial will be dependent upon subjects' supplying a newly obtained core or excisional biopsy of a tumor lesion and/or tissue from an archival tissue sample to evaluate for PD-L1 expression by IHC. The specimen will be evaluated at a central laboratory for expression status of PD-L1. Subjects with PD-L1 positive and PD-L1 negative tumors will be enrolled in Cohorts 1 and 2, approximately 200 combined. The prediction of response to anti-PD-1 therapy is based on the results from Topalian et al [36] who examined PD-L1 expression in the archival specimens of 42 of the 296 subjects treated with the PD-1 inhibitor nivolumab. Of those 17 subjects whose tumor cells did not stain positive for PD-L1 using a 5% threshold of tumor cell surface expression, no objective response by RECIST 1.1 was observed. But among the 25 subjects whose tumor cells were considered positive for PD-L1, 9 responded (36%). Therefore, it is hypothesized that PD-L1 expression may be a predictive biomarker of anti-PD-1 activity, and subjects will be allocated by PD-L1 expression in this study.

An emerging body of evidence suggests that post-transcriptional modification of androgen receptor message RNA may mediate resistance to targeted endocrine therapy. One such example appears to be by modification to androgen-receptor isoform encoded by splice variant 7, which lacks the androgen-binding domain [37].

Cohorts 4 and 5 will explore the efficacy of pembrolizumab in chemotherapy-naïve subjects with mCRPC who are receiving pre-chemotherapy enzalutamide. Bishop et al. demonstrated in a mouse xenograft model that enzalutamide-resistant tumors express significantly increased levels of tumor intrinsic PD-L1 compared to non-enzalutamide resistant tumors [38]. Additionally, in a small cohort of subjects, it was noted that those who progressed while on enzalutamide had a significantly increased number of PD-L1/2-positive dendritic cells in their blood compared to treatment-naïve subjects or subjects who were responding to enzalutamide. Thus, by blocking PD-L1, pembrolizumab treatment may increase the immune response to the enzalutamide-resistant cells that emerge in response to treatment with enzalutamide.

The PSA response rate of subjects treated with enzalutamide after abiraterone may be modest, as judged by a retrospective study of subjects with mCRPC who received various prior sequences of abiraterone, docetaxel, and enzalutamide [39]. The results showed that the group that received enzalutamide after abiraterone (N = 79) demonstrated a 50% or greater PSA decline in 18% of subjects. The median OS was reached only for subjects in the prior abiraterone plus docetaxel group and was 12.2 months. However, in another retrospective study evaluating the PSA response of enzalutamide or docetaxel treatment after abiraterone, the enzalutamide arm (N = 30) demonstrated a 50% or greater PSA decline in 34% of subjects [40]. The median PFS was 4.1 months and the median PFS was 4.7 months. Overall survival was not described. Preliminary safety and efficacy data are available from a recent Phase 2 study (NCT0231255). Twenty-eight subjects with mCRPC were enrolled. The primary endpoint was a ≥50% PSA reduction. Early data were published in June 2016 on the first 10 patients enrolled [41]. Three of the 10 patients enrolled and with at least 4 months of follow-up achieved complete biochemical responses based on the primary endpoint. All responders continued their profound biochemical response, as well as clinical partial response for those with soft tissue target lesions and no sign of progression for those with bone metastases. These encouraging new data support a further validation as proposed for Cohorts 4 and 5 to better understand which patient populations respond to pembrolizumab in the short and long term.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg Q3W. The **initial dose approved by the Food and Drug Administration (FDA) for treatment of** melanoma subjects was 2 mg/kg Q3W. Currently, clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W. The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized mAbs, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other subject covariates on exposure using available data from 1139 subjects (from KN001 and KN002) has been performed. The majority of these subjects (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the antitumor 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 solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the antitumor activity of pembrolizumab in subjects with mCRPC previously treated with chemotherapy. Objective response rate will be used as the primary endpoint, and objective response will be determined using RECIST 1.1 by the central imaging vendor in the measurement of soft tissue disease. Duration of response and PFS will be determined using radiographic progression. Radiographic progression for soft tissue lesions will be determined using RECIST 1.1 (Section 12.7). Radiographic progression for bone lesions will be determined by radionuclide bone scan using the consensus guidelines of the PCWG3 criteria [42, 43]. Time-to-progression endpoints, including DOR, DCR, and rPFS, will be measured until progressive disease (PD) to be defined as the point at which there has been tumor progression in soft tissue lesions by RECIST 1.1 guidelines and/or tumor progression in bone lesions detected by radionuclide bone scan by PCWG criteria (PCWG3-modified RECIST 1.1).

4.2.3.1.1 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. 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. Thus, standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of patients with MEL enrolled in KN001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had PD by RECIST 1.1 but not by immune-related RECIST criteria (irRECIST) had longer OS than patients with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression.

irRECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immunotherapeutics. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by central imaging vendor in support of the exploratory ORR and DCR endpoints. Progressive disease in bone will be assessed using radionuclide bone scan in accord with PCWG3 criteria (PCWG3-modified irRECIST).

4.2.3.2 Patient Reported Outcomes

EQ-5D and FACT-P are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.3.2.1 eEuroQoL-5D (eEQ-5D)

The eEQ-5D is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years (QALYs). The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [44]. Each dimension is rated on a three-point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The eEQ-5D should be completed by subjects first and followed by the FACT-P.

4.2.3.2.2 The Functional Assessment of Cancer Therapy-Prostate (FACT-P)

FACT-P questionnaire is a relevant, worldwide tool used for assessing the health-related quality of life (HRQOL) in men with prostate cancer [45]. Developed as a disease-specific adjunct to the FACT measurement system, FACT-P consists of FACT-G (general) which contains a 27-item self-report questionnaire measuring general HRQoL in four domains (physical, social, emotional, and functional well-being) and 12 prostate cancer-specific items. FACT-P (version 4) is self–administered and requires approximately 8 to 10 minutes to complete.

4.2.3.3 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with mCRPC previously treated with docetaxel-based chemotherapy (Cohorts 1, 2, and 3) and in subjects with mCRPC failing or showing early signs of failing on current enzalutamide treatment (Cohorts 4 and 5). The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria (Appendix 12.6). Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including SAEs and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including, but not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.3.4 Pharmacokinetic Endpoints

Blood samples will be obtained to measure the PK of pembrolizumab for Cohorts 1 through 3. The pembrolizumab serum plasma maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times may be summarized.

Pharmacokinetic data may also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study as well as PK data obtained from other studies (if available), a population PK analysis could be performed to characterize PK parameters (clearance (CL), volume of distribution (V)) and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen. Pharmacokinetic data may also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy, as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

4.2.3.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of adverse events in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (blood components, tumor material, etc.) to support analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) Genetic Analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical

trial population correlates with response to the treatment 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. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

Genetic (DNA) analyses from tumor: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability, etc). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome. Microsatellite instability (MSI) may also be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

Tumor and blood RNA analyses: Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing IFN-γ transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL-10). MicroRNA profiling may also be pursued.

Proteomics and Immunohistochemistry (IHC) using Blood or Tumor: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in-vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., TNBC, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

Other Blood-derived Biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a

major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.3.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male subjects at least 18 years of age with mCRPC will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be ≥18 years of age on day of signing informed consent.

3. Have histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology. Diagnosis must be stated in a pathology report and confirmed by the Investigator.

4. Have RECIST 1.1-measurable prostate cancer on computed tomography (CT) or magnetic resonance imaging (MRI) scans (Cohorts 1, 2, and 4) or detectable bone metastases by whole body bone scintigraphy and no RECIST 1.1-measurable tumors (Cohorts 3 and 5), as determined by central review. Disease must be either metastatic or locally confined inoperable disease that cannot be treated with definitive intent.

5. Have supplied tumor tissue from a newly obtained biopsy or provided a tumor tissue specimen ≤12 months prior to the screening date and an archival specimen, if available, from a site not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization; other exceptions may be considered after Sponsor consultation). Adequacy of these specimens for PD-L1 biomarker analysis will be required by a central laboratory prior to enrollment. Subjects in Cohorts 1, 2, and 4 with visceral/measurable lesions must provide a newly obtained biopsy performed after the last line of systemic therapy where safely available or a specimen obtained ≤12 months prior to the screening date and an archival specimen, if available. Subjects in Cohort 3 and 5 must at least provide an archival specimen.

Note: Tumor blocks are preferred. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut.

For Cohorts 1, 2, and 3 only:

6. Have been treated with:

   a. At least one targeted endocrine therapy (defined as second generation antiandrogen therapies that include but are not limited to abiraterone acetate with prednisone, enzalutamide, and next generation targeted agents such as ARN-509). [Note: First generation antiandrogens such as flutamide, nilutamide, bicalutamide are not included in this group.]

   b. At least one regimen/line of chemotherapy that contained docetaxel.

   c. No more than two chemotherapy regimens.

   d. No more than three regimens/lines of the aforementioned treatments (having failed/progressed on chemotherapy and targeted endocrine therapy).

For Cohorts 4 and 5 only:

7. For chemotherapy-naïve subjects with mCRPC either having failed or showing early signs of failing on enzalutamide treatment as defined by PCWG3 guidelines (eg, signs of clinical progression, increased alkaline phosphatase, PSA increase, or positive imaging assessments). Subjects can have failed prior abiraterone treatment before current enzalutamide treatment. Subjects must have had a clinically

meaningful response to enzalutamide treatment. Enzalutamide must have been initiated no less than 4 weeks prior to the first dose of trial treatment and be continued throughout the study.

All Cohorts:

8. Have documented prostate cancer progression within 6 months prior to screening, as determined by the Investigator, by means of one of the following:

   a. PSA progression as defined by a minimum of 3 rising PSA levels with an interval of ≥1 week between each assessment where the PSA value at screening should be ≥2 ng/mL.

   b. Radiographic disease progression in soft tissue or bone with or without PSA progression

9. Have ongoing androgen deprivation with total serum testosterone < 50 ng/dL (< 2.0 nM). If the subject is currently being treated with LHRH agonists (subjects who have not undergone an orchiectomy), this therapy must have been initiated at least 4 weeks prior to first dose of trial treatment. This treatment must be continued throughout the study.

10. Subjects receiving bone resorptive therapy (including but not limited to bisphosphonate or RANK-L inhibitor) must have been on stable doses for ≥ 4 weeks prior to first dose of trial treatment.

11. Have a performance status of 0, 1, or 2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 12.5).

12. Subjects are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception after the last dose of enzalutamide is 30 days.

    Subjects must either:

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

    OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), as detailed below:

      - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP (see Section

12.8) who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Note: The above contraception requirements also apply to participants currently receiving study drugs at the time of Amendment 07.

Note: No contraception is necessary for participants who will receive pembrolizumab monotherapy (Second Course treatment).

13. Demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	>1,500.0/μL
Platelets[a]	≥100,000.0/μL
Hemoglobin[a]	≥9.0 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GRF can also be used in place of creatinine or creatinine clearance)	≤1.5 × upper limit of normal (ULN) **OR** ≥60.0 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Serum Total Bilirubin	≤ 1.5 × ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN **OR** ≤5 × ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT); Partial Thromboplastin Time (PTT) or 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 ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

a. Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (granulocyte colony stimulating factor - GCSF or erythropoietin) within 2 weeks prior to treatment initiation.

b. Creatinine clearance should be calculated per institutional standard.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of trial treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (replacement therapy for adrenal insufficiency is permitted).

   Note: Treatment with palliative prednisone such as 10 mg daily or corticosteroid equivalent in the manner used to treat men with prostate cancer is permitted without Sponsor notification.

3. Has had a prior anti-cancer mAb within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to mAbs administered more than 4 weeks earlier.

4. Has had prior chemotherapy, targeted small molecule therapy, or external beam radiation therapy within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent. Treatment with Radium-223 is allowed as long as the last dose has been administered no less than 4 weeks prior to the first dose. Note: Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of trial treatment.

5. Has a known additional malignancy that has had progression or has required active treatment in the last 3 years. Exceptions include basal cell carcinoma of the skin, and squamous cell carcinoma of the skin that has undergone potentially curative therapy.

6. Has known active central nervous system (CNS) 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 the first dose of trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

8. Has evidence of interstitial lung disease and/or a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

9. Has an active infection requiring systemic therapy.

10. 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.

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

12. Has previously participated in any other pembrolizumab (MK-3475) trial, or received prior therapy with an anti-PD-1, anti-PD-L1, and anti-PD-L2 (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

15. Has received a live vaccine within 30 days of planned start of study therapy.

    Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

Additionally, the following apply to Cohorts 4 and 5 only:

16. Has received prior chemotherapy (e.g., docetaxel) for mCPRC.

17. Has any condition (cardiac, neurologic, absorption) other than clinically failing or showing early signs of failing on enzalutamide treatment that would require imminent discontinuation of enzalutamide treatment.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Sourcing
Pembrolizumab (MK-3475)	Solution for infusion	100 mg per vial	200 mg Q3W	IV infusion	Central
Abbreviations: IV = intravenous; N/A = not applicable; Q3W = every 3 weeks; QD = every day.					

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.1.2.1 Pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 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 in Table 3.

Table 3 Dose Modification and Treatment Discontinuation Guidelines for Immune-related Adverse Events 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.

irAEs	**Toxicity grade or conditions (NCI CTCAE v4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants 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 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) 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		

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; NCI = National Cancer Institute; T1DM = type 1 diabetes mellitus.

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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 (e.g., 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 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5 h (±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).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** 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
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v4.0 at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. 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

5.2.2.1 Pembrolizumab

The first infusion should be administered on the day of treatment allocation or as close as possible to the date on which the subject is allocated, ie, ≤7 days. Pembrolizumab should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6). After the first cycle, trial treatment may be administered up to 3 days before or after the scheduled Day 1 of the cycle due to administrative reasons.

Details pertaining to the preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

Treatment allocation will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). All eligible subjects will be allocated to receive pembrolizumab 200 mg Q3W as monotherapy. Subjects enrolled in Cohorts 4 and 5 will remain on their current stable SOC dose of enzalutamide therapy during pembrolizumab monotherapy. Enzalutamide will not be supplied by the sponsor.

5.4 Stratification

All eligible subjects will be enrolled into one of the cohorts in this study based on treatment history, PD-L1 status for Cohorts 1 and 2 only, and RECIST 1.1 measurability.

No additional stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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 Clinical Director. 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.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Subject may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants.

For Cohorts 4 and 5, the use of enzalutamide will be recorded on the CRF. If dose modification of enzalutamide is required during the trial period, documentation of dosage should also be included on the CRF.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- GM-CSF
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Palliative localized radiation therapy to a site of pre-existing disease may be permitted while on study after consultation with Sponsor. The radiation treatment field may not include a target or measurable lesion by RECIST 1.1. Pre-existing treatment with Radium-223 dichloride is allowed so long as the last dose has been administered no fewer than 4 weeks from the first dose of trial drug.

- 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, chickenpox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Inhaled steroids for management of asthma are permitted.

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) is permitted.

  Note: Treatment with palliative prednisone such as 10 mg daily or corticosteroids equivalent in the manner used to treat men with prostate cancer is permitted.

  Note: Physiologic doses of corticosteroids for adrenal insufficiency are permitted.

Subjects who, in the assessment by the investigator and after consultation with the Sponsor, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase. Subjects must be discontinued from the active follow-up phase if they begin a non-trial treatment for their underlying disease.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, Table 3. Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 5.2.1.2 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.

5.6.2 Radiotherapy

The use of radiotherapy or surgical intervention while on study must be recorded in the trial database.

Localized palliative radiation therapy to a site of pre-existing disease may be permitted while on study. However, if the subject develops a new lesion or a definite increase in the size of existing bone or visceral lesions with or without extension into the soft tissue that meets the criteria for disease progression according to PCWG3, treatment must be discontinued for PD regardless of whether radiation therapy is initiated.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Post Treatment.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the subject at unnecessary risk from continued administration of study drug.
- The subject has a positive urine drug screen at any time during the course of the trial.
- Documented disease progression as assessed by the investigator using PCWG3-modified RECIST 1.1 guidelines (Section 7.1.2.6.1 – Initial Tumor Imaging). Two consecutive assessments are needed for disease progression. Clinical deterioration will not be considered progression.
- Unacceptable adverse experiences as described in Section 5.2.1.2 – Dose Modification (Escalation/Titration/Other) and Section 5.6.1 – Supportive Care Guidelines
- Intercurrent illness that prevents further administration of treatment
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons

Cohorts 4 and 5: If subjects have to discontinue enzalutamide treatment after being enrolled into the study due to adverse events or toxicity attributed to enzalutamide, subjects can continue to receive pembrolizumab as long as they experience clinical benefit without signs of disease progression and tolerable safety.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

Subjects may be allowed to begin treatment again if deemed medically appropriate.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete,
2. Poor adherence to protocol and regulatory requirements,
3. Plans to modify or discontinue the development of the study drug pembrolizumab.

In the event of Sponsor decision to no longer supply study drug pembrolizumab, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles[b]**								**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)[a]	1	2	3	4	5	6	7	8	DC	Safety Follow-up[c]	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days):	-42 to -1		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days after last dose (±3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures													
Informed Consent	X[f]												
Informed Consent for FBR (optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X (dispense)									X (collect)			
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X[g]	X	X	X	X	X	X	X	X	X	X[g]		
Trial Treatment Administration		X[h]	X	X	X	X	X	X	X				
Subsequent Anticancer Therapy Status												X	X
Survival Status[i]		←	----------	----------	----------	----------	----------	----------	----------	→		← ---------- →	X
Clinical Procedures/Assessments													
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	
Full Physical Examination[k]	X									X			
Directed Physical Examination[k]		X	X	X	X	X	X	X	X				
Vital Signs and Weight[l]	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X[m]	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
PT/INR and PTT/aPTT	X[n]												
CBC with Differential[o]	X[n]		X	X	X	X	X	X	X	X	X[p]		
Comprehensive Chemistry Panel[o]	X[n]		X	X	X	X	X	X	X	X	X[p]		
Urinalysis[o,q]	X[n]		X[q]		X		X		X	X	X[p]		
T3, FT4 and TSH[o]	X[n]		X[q]		X		X		X	X	X[p]		

Trial Period:	Screening Phase	Treatment Cycles[b]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)[a]	1	2	3	4	5	6	7	8	DC	Safety Follow-up[c]	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days):	-42 to -1		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days after last dose (±3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Total Testosterone[o]	X[n]				X[r]				X	X			
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory													
Tumor Marker Assessment (PSA)[s]	X				X			X		X		X	
PSA for Cohorts 4 and 5[s]	X		X	X	X			X		X		X	
Anti-drug Antibodies (ADA)[t]		X	X		X		X		X				
Pembrolizumab Pharmacokinetics (serum)[t]		X[u]	X		X		X		X				
Blood for CTC		X[v, w]								X			
Blood for AR-V7[v]		X											
Efficacy Measurements													
Tumor Imaging[s] (CT/MRI/bone scan)	X[x]				X			X		X[y]		X[z]	
Tumor Tissue Collection/Correlative and Biomarker Studies													
Tumor Tissue Collection (Newly Obtained and Archival)	X[aa]												
Blood for Genetic Analyses		X[bb]											
Blood RNA Analyses[cc]		X	X			X				X			
Blood for Plasma Biomarker Analyses[cc]		X	X			X				X			
Blood for Serum Biomarker Analyses[cc]		X	X			X				X			
Blood for ctDNA (plasma)[dd]		X			X			X		X			
Patient Reported Outcomes													
EuroQol EQ-5D[ee]		X	X	X	X			X		X	X		
FACT-P[ee]		X	X	X	X			X		X	X		

Trial Period:	Screening Phase	Treatment Cycles[b]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)[a]	1	2	3	4	5	6	7	8	DC	Safety Follow-up[c]	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days):	-42 to -1		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days after last dose (±3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; AR-V7 = androgen receptor variant 7; CBC = complete blood count; CT = computed tomography; CTC = circulating tumor cells; ctDNA = circulating tumor cell DNA; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FACT-P = functional assessment of cancer therapy-prostate; FBR = future biomedical research; FT4 = free thyroxine; INR = international normalized ratio; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid stimulating hormone.

a. Subjects may only be rescreened once.

b. All treatment cycles are 3 weeks ± 3 days.

c. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the start of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

d. Follow-up visits must occur using the same imaging schedule the subject was on during treatment (eg, every 9 weeks [63 days ±7 days] from the date of allocation or every 12 weeks [84 days ±7 days] from the date of allocation). In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (CT/MRI and bone scans) and PSA according to the schedule that the subject was on at the time of discontinuation (eg, every 9 or 12 weeks from the date of allocation) until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death or 4) the end of the study, whichever occurs first.

e. Survival follow-up begins 12 weeks from the time a subject experiences confirmed disease progression or starts a new anti-cancer treatment.

f. Written consent must be obtained prior to performing any protocol specified procedures. Results of a test performed prior to the subject signing consent are acceptable in lieu of new screening tests if they are a part of routine clinical management and performed within the specified timeframe.

g. Prior medications: record all medications taken within 28 days prior to the first dose of trial treatment. Concomitant medications: enter new medications started during the trial and up to 30 days after last dose of trial treatment regardless of when the safety follow-up visit occurs. All medications related to reportable SAEs and events of clinical interest (ECIs) should be recorded as defined in Section 7.2.

h. Trial treatment should begin on the day of treatment allocation or as close as possible to the date on which the subject is allocated, ie, ≤7 days.

i. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

j. Record all AEs (including ECIs) occurring up to 30 days after the last dose of trial treatment. SAEs must be recorded up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject starts new anti-cancer treatment. Treatment related SAEs must always be reported.

Trial Period:	Screening Phase	Treatment Cycles[b]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)[a]	1	2	3	4	5	6	7	8	DC	Safety Follow-up[c]	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days):	-42 to -1		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days after last dose (±3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)

k. A full physical exam will be performed at screening and at treatment discontinuation; all treatment visits will include a directed physical exam.

l. Height will be measured at screening only.

m. Following Cycle 8, ECOG Performance Status will be performed at every other cycle (Cycles 10, 12, 14,…) and at treatment discontinuation.

n. Laboratory procedures at screening are to be performed within 10 days prior to the first dose of trial treatment.

o. After Cycle 1, pre-infusion laboratory procedures may be conducted up to 72 hours pre-infusion.

p. Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.

q. Urinalysis and thyroid function testing are done at screening, every other cycle (Cycles 2, 4, 6,…), treatment discontinuation, and the safety follow-up visit.

r. Total testosterone will be done at screening, every fourth cycle (Cycles 4, 8, 12,…) and at treatment discontinuation

s. Imaging assessments (CT/MRI and bone scans) and PSA should be performed every 9 weeks (63 days ±7 days) for the first year (through week 54), every 12 weeks (84 days ±7 days) in the second year, at treatment discontinuation and during follow-up. The timing of these assessments should not be adjusted for dose delays or cycle starts. For Cohorts 4 and 5, screening PSA by central results are required prior to allocation. PSA should be performed Q3W until Cycle 4.

t. Pre-infusion (trough) PK and anti-pembrolizumab antibody (ADA) samples will be collected within 24 hours before infusion at Cycles 1, 2, 4, 6, and 8. To be collected from subjects in Cohorts 1 to 3 only.

u. Post-dose (peak) PK samples will be drawn within 30 minutes after the end of infusion at Cycles 1 and 8. Additional single PK samples should be drawn at the following time points after Cycle 1 dosing: 24 hours (±4 hours) [Day 2], between 72 and 168 hours [Day 4-8], and 336 hours (±48 hours) [Day 15]. To be collected from subjects in Cohorts 1 to 3 only.

v. Blood for AR-V7 and blood for CTC can be collected up to 3 days prior to infusion at Cycle 1. Leftover samples will be kept for future biomedical research if the subject signs the FBR consent.

w. Leftover samples may be kept for FBR if the subject signs the FBR consent.

x. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment.

y. If a scan was obtained within 4 weeks prior to treatment discontinuation, then another scan at discontinuation is not mandatory. Radiological evaluation should be repeated at treatment discontinuation in subjects discontinuing without confirmed disease progression (date of discontinuation ±4 weeks).

z. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (CT/MRI and bone scans) and PSA according to the schedule that the subject was on during study treatment (eg, every 9 weeks [63 days ±

Trial Period:	Screening Phase	Treatment Cycles[b]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)[a]	1	2	3	4	5	6	7	8	DC	Safety Follow-up[c]	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days):	-42 to -1		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days after last dose (±3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)

7 days] from the date of allocation or every 12 weeks [84 days ± 7 days] from the date of allocation) until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death or 4) the end of the study, whichever occurs first.

aa. Baseline tumor tissue for biomarker analysis from an archival tissue sample and/or newly obtained core or excisional biopsy (fine needle aspirate not adequate) must be sent to the testing laboratory and analyzed for adequacy prior to enrollment. Refer to Section 7.1.2.7 for details on newly obtained biopsy and/or archival specimen requirements by cohort.

bb. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

cc. Blood for RNA Analyses and Blood for Serum/Plasma Biomarker Analyses should be collected pre-infusion according to time points on the flow chart. Collections end at cycle 5 and should not be repeated. Leftover samples may be kept for FBR if the subject signs the FBR consent.

dd. Blood for ctDNA can be collected up to 3 days prior to the Cycle 1 pre-infusion (if the collection coincides with a treatment cycle) every 9 weeks (63 days ±7 days) for the first year (through week 54), every 12 weeks (84 days ±7 days) in the second year, and at treatment discontinuation. The timing of these assessments should not be adjusted for dose delays or cycle starts. Leftover samples may be kept for Future Biomedical Research if the subject signs the FBR consent.

ee. Electronic patient reported outcomes (ePROs) should ideally be administered prior to all study procedures (EQ-5D first, followed by FACT-P). All ePROs are to be administered pre-infusion at Cycles 1, 2, 3, and 4 and every 3 cycles thereafter (Cycle 7, 10, 13, 16, and 19), at treatment discontinuation, and again 30 days after last dose of trial treatment. If the subject does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

6.2 Second Course Phase (Retreatment ONLY)

Trial Period:	SECOND COURSE PHASE: Treatment Cycles[a]								End of Treatment	Post-Treatment		
					To be repeated beyond 8 cycles							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	DC	Safety Follow-up[b]	Follow Up Visits[c]	Survival Follow-Up[d]
Scheduling Window (Days):		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days from last dose (±3 days)	Every 9 weeks (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures												
Eligibility Criteria[e]	X											
Concomitant Medication Review[f]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration	X	X	X	X	X	X	X	X				
Subsequent Anticancer Therapy Status											X	X
Survival Status[g]	<----------							---------->		<----------	---------->	X
Clinical Procedures/Assessments												
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X[h]	X[h]	
Full Physical Examination[i]	X								X			
Directed Physical Examination[i]		X	X	X	X	X	X	X				
Vital Signs and Weight	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X[j]	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
PT/INR and PTT/aPTT	X[k]											
CBC with Differential[l]	X[k]	X	X	X	X	X	X	X	X	X[m]		
Comprehensive Chemistry Panel[l]	X[k]	X	X	X	X	X	X	X	X	X[m]		
T3, FT4 and TSH[l]	X[k]		X[n]		X		X		X	X[m]		
Urinalysis[l]	X[k]		X[n]		X		X		X	X[m]		
Total Testosterone[l]	X[k]			X[o]				X	X			
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory												
Tumor Marker Assessment (PSA)[p]	X			X			X		X		X[c]	
Efficacy Measurements												
Tumor Imaging[p] (CT/MRI/bone scan)	X[q]			X			X		X[r]		X[c]	

Trial Period:	SECOND COURSE PHASE: Treatment Cycles[a]								End of Treatment	Post-Treatment		
					To be repeated beyond 8 cycles							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	DC	Safety Follow-up[b]	Follow Up Visits[c]	Survival Follow-Up[d]
Scheduling Window (Days):		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days from last dose (±3 days)	Every 9 weeks (±7 days)	Every 12 weeks (±7 days)

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CBC = complete blood count; CT = computed tomography; DC = discontinuation; ECOG = Eastern Cooperative Oncology Group; FT4 = free thyroxine; INR = international normalized ratio; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid stimulating hormone.

a. All treatment cycles are 3 weeks ± 3 days.

b. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the start of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

c. Follow-up visits must occur every 9 weeks (63 days ±7 days) from the date of last dose of study treatment. In subjects who discontinue therapy without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging (CT/MRI and bone scans) and PSA until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death or 4) the end of the study, whichever occurs first.

d. Survival follow-up begins 12 weeks from the time a subject experiences confirmed disease progression or starts a new anti-cancer treatment.

e. Subjects may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.

f. Report new medications started during the trial and up to 30 days after last dose of trial treatment regardless of when the safety follow-up visit occurs. All medications related to reportable SAEs and events of clinical interest (ECIs) should be recorded as defined in Section 7.2.

g. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

h. Record all AEs (including ECIs) occurring up to 30 days after the last dose of trial treatment. SAEs must be recorded up to 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject starts new anti-cancer treatment. Treatment related SAEs must always be reported.

i. A full physical exam will be performed prior to subject receiving first retreatment infusion and at treatment discontinuation; all treatment visits will include a directed physical exam.

j. Following Cycle 8, ECOG Performance Status will be performed at every other cycle (Cycles 10, 12, 14,…) and at treatment discontinuation.

k. Laboratory tests are to be performed within 10 days prior to subject receiving first retreatment infusion.

l. After Cycle 1, pre-infusion laboratory procedures may be conducted up to 72 hours pre-infusion.

m. Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.

n. Urinalysis and thyroid function testing are performed within 10 days prior to first retreatment infusion, every other cycle (Cycles 3, 5, 7,…), treatment discontinuation, and the safety follow-up visit.

Trial Period:	SECOND COURSE PHASE: Treatment Cycles[a]								End of Treatment	Post-Treatment		
					To be repeated beyond 8 cycles							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	DC	Safety Follow-up[b]	Follow Up Visits[c]	Survival Follow-Up[d]
Scheduling Window (Days):		±3	±3	±3	±3	±3	±3	±3	At time of DC	30 days from last dose (±3 days)	Every 9 weeks (±7 days)	Every 12 weeks (±7 days)

o. Total testosterone will be done within 10 days prior to first retreatment infusion, every fourth cycle (Cycles 4, 8, 12,…) and at treatment discontinuation.

p. Imaging assessments (CT/MRI and bone scans) and PSA should be performed every 9 weeks (63 days ±7 days), at treatment discontinuation and during follow-up. The timing of these assessments should not be adjusted for dose delays or cycle starts.

q. Imaging assessment must be performed within 28 days prior to the subject receiving first retreatment infusion. Scans performed as part of routine clinical management are acceptable if they are of diagnostic quality and performed within 28 days prior to the first dose of retreatment.

r. If a scan was obtained within 4 weeks prior to treatment discontinuation, then another scan at discontinuation is not mandatory. Radiological evaluation should be repeated at treatment discontinuation in subjects discontinuing without confirmed disease progression (date of discontinuation ±4 weeks)

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will include all active conditions and any conditions diagnosed within the prior 10 years that are considered clinically significant by the Investigator. Details pertaining to the subject's prostate cancer diagnosis will be recorded separately and not listed as medical history.

7.1.1.4.1 History of Prostate Cancer

The investigator or qualified designee will obtain information regarding the subject's prostate cancer. This information will include but is not limited to the presentation at primary diagnosis, date and stage at primary diagnosis, date of and stage at most recent recurrence, and location of metastases at screening (if applicable).

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior medication taken by the subject within 28 days prior to the first dose of trial treatment.

7.1.1.5.2 Prior Treatment for Prostate Cancer

The investigator or qualified designee will review and report all prior treatments to prostate cancer including systemic treatments, radiation, and surgeries**.**

7.1.1.5.3 Concomitant Medications

The investigator or qualified designee will record medications taken by the subject during the trial up to 30 days after the last dose of trial treatment. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5.4 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the start of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated by non-random assignment and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

Upon study completion, participants are discontinued from the current study and may be transitioned into a pembrolizumab extension study, if available. All participants in the extension study will be allocated by non-random assignment and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. This number will be unique from the treatment/ randomization number in the parent study.

7.1.1.8 Trial Compliance (Medication)

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab (MK-3475) doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if they are events with potential immunologic etiology. See Section 5.6.1 regarding the identification, evaluation, and management of AEs of a potential immunological etiology.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and at treatment discontinuation. Clinically significant abnormal findings at screening should be recorded as medical history. New clinically significant abnormal findings at treatment discontinuation should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam, as clinically indicated, prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

The investigator or qualified designee will assess vital signs at screening, prior to dosing on Day 1 of each treatment cycle and at treatment discontinuation. Vital signs include temperature, heart rate, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 12-Lead ECG

A standard 12-lead ECG will be performed once at the screening visit using local standard procedures. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG Performance Status (see Section 12.5) at screening and prior to dosing on Day 1 of each treatment cycle through Cycle 8. After Cycle 8, ECOG Performance Status will be assessed at every other cycle (Cycles 10, 12, 14) and at treatment discontinuation.

7.1.2.6 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM).

Tumor imaging should be acquired by CT (strongly preferred) and radionuclide bone scan. Magnetic resonance imaging should be used where CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden. Tumor imaging by both CT (or MRI) and radionuclide bone scan is required at every scheduled imaging time point.

All scheduled images for all subjects must be submitted to the central imaging vendor. Imaging obtained at unscheduled time points must also be sent to the central imaging vendor if the images support new or worsening metastatic disease based on site assessment.

Central review of baseline scans will be used to determine cohort assignment. Local review of imaging will be used for subject management. The central imaging vendor will receive radiologic images during the course of the study and will perform an analysis of response to treatment.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of first dose of trial treatment. Tumor imaging by both CT (or MRI) and radionuclide bone scan is required at screening.

Scans performed as part of routine clinical management are acceptable for use as the screening scans if they are of diagnostic quality, performed within 28 days prior to the date of first dose of trial treatment and can be assessed by the central imaging vendor.

Confirmation of measurable disease per RECIST 1.1 by central imaging vendor will be used to determine cohort assignment. Subjects with measurable disease per RECIST 1.1 will be enrolled in Cohorts 1, 2, and 4. Subjects with detectable bone metastases by whole body bone scintigraphy and no RECIST 1.1-measurable tumors will be enrolled in Cohorts 3 and 5.

The Sponsor allows for evaluation and follow-up of up to 10 soft tissue lesions (RECIST 1.1).

At screening, all lesions seen by CT (or MRI) and radionuclide bone scan will be documented. In determining response to treatment or progression, investigators must evaluate all target and non-target lesions and search for new lesions at each imaging time point.

7.1.2.6.2 Tumor Imaging During Trial

In the first year, on study imaging assessments must be performed every 9 weeks (63 days ±7 days) from the date of allocation for the first year (through week 54 ± 7 days). Subjects who remain on treatment beyond the first year will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days from date of allocation and should not be adjusted for delays in cycle starts.

Response

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date response was first documented. The scan for confirmation of response may be performed ≥4 weeks after the first indication of response or at the next scheduled scan, whichever is clinically indicated. Subjects who obtain a repeat scan do not need to undergo the next scheduled imaging if it is <4 weeks after the confirmation scan. Subjects will return to their regular imaging schedule starting with the next time point.

For any subject with known brain metastases at baseline, and who achieves a CR during trial treatment, a follow-up brain scan is required for confirmatory assessment of CR.

Progression

Radiographic progression for soft tissue lesions will be determined according to RECIST 1.1 (Section 12.7). Disease progression in soft tissue lesions should be confirmed by the site ≥4 weeks after the first radiologic evidence of PD. Subjects who have unconfirmed disease progression and are clinically stable may continue on treatment at the discretion of the investigator until progression is confirmed by the site. Subjects who obtain a repeat scan do not need to undergo the next scheduled imaging if it is < 4 weeks after the confirmation scan. Subjects will return to their regular imaging schedule starting with the next time point.

Subjects who have confirmed disease progression, as assessed by the site, will discontinue treatment.

Radiographic progression for bone lesions will be determined as described in the consensus guidelines of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) [44]. Radiographic progression of bone lesions will be defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. Progression in bone at the first scheduled assessment at Week 9, if unaccompanied by soft tissue progression, requires a second radionuclide bone scan ≥6 weeks later. Progression is confirmed to have occurred at the first scheduled assessment if the confirmation bone scan shows ≥2 additional new lesions. Radiographic bone progression after the 9 week assessment must be confirmed ≥6 weeks later, if unaccompanied by soft tissue progression. Progression is confirmed if the confirmation bone scan shows the persistence of ≥2 new bone lesions. Subjects who have unconfirmed disease progression and are clinically stable may continue on treatment at the discretion of the investigator until progression is confirmed by the site. Subjects who have confirmed disease progression, as assessed by the site, will discontinue treatment.

If a subject with confirmed radiographic progression is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions and no additional new lesions develop (non-worsening PD) to continue study treatment.

Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent or death, whichever occurs first (Table 5).

Table 5 Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks to confirm PD (soft-tissue progression) Repeat bone scan at ≥6 weeks to confirm PD (bone progression)	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥4 weeks to confirm PD if possible (soft-tissue progression) Repeat bone scan at ≥6 weeks to confirm PD if possible (bone progression)	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.6)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 9 weeks (every 12 weeks after 12 months)	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 9 weeks (every 12 weeks after 12 months)	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

7.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation another scan at treatment discontinuation isn't mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule the subject was on during treatment (e.g. every 9 weeks [63 days ±7 days] from the date of allocation or every 12 weeks [84 days ±7 days] from the date of allocation) until: 1) the start of new anti-cancer treatment, 2) disease progression, 3) death or 4) the end of the study, whichever occurs first.

7.1.2.6.4 Second Course (Retreatment) Tumor Imaging

A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging should be submitted to the central imaging vendor for retrospective review.

On study imaging assessments should be performed every 9 weeks (63 days ±7 days) after the restart of treatment or more frequently if clinically indicated.

If tumor imaging shows initial PD (Section 7.1.2.6.), tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Per PCWG3, if radionuclide bone scan shows progression in bone, a radionuclide bone scan should be repeated ≥6 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation bone scan do not need to undergo the next scheduled bone scan and may wait until the next scheduled time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.

In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging using the same schedule the subject was on during treatment (e.g. every 9 weeks from the date of allocation or every 12 weeks [63 days ±7 days] from the date of allocation) until: 1) the start of new anti-cancer treatment, 2) disease progression, 3) death or 4) the end of the study, whichever occurs first.

7.1.2.6.5 Treatment Beyond Progression

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy and then experience subsequent disease response. Subjects that are deemed clinically unstable are not

required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In subjects who have shown initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects who are clinically stable may continue receiving study therapy until PD is confirmed by repeat imaging assessments. Progression in soft tissue lesions should be confirmed by the site ≥4 weeks after the first radiologic evidence of PD. Progression in bone should be confirmed by the site ≥6 weeks after the first radiologic evidence of PD. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
2) No decline in ECOG performance status
3) Absence of rapid progression of disease
4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Any subject deemed **clinically unstable** should be discontinued from trial treatment at site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur:

- Target lesion sum of diameters is <20 % or <5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat imaging does not confirm PD as assessed by the local site investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur:

- Target lesion sum of diameters remains ≥20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

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

NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating PD), 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 6.0 Study Flowchart and be submitted to the central imaging vendor.

7.1.2.7 Tumor Tissue Collection

Participation in this trial will be dependent upon subjects' supplying tumor tissue for PD-L1 biomarker analysis from a site not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization; other exceptions may be considered after Sponsor consultation). Adequacy of these specimens for PD-L1 biomarker analysis will be required by a central laboratory prior to enrollment.

Subjects in Cohorts 1, 2, or 4 with visceral/measurable lesions must provide a newly obtained biopsy where safely available and an archival specimen, if available. Candidates for enrollment into Cohort 1, 2, or 4 who undergo a study-related biopsy but the tissue sample is determined to be inadequate will be allowed onto the study if they have provided an adequate archival specimen. Subjects in Cohorts 3 and 5 must at least provide an archival specimen. Subjects whose tumor tissue is adequate for PD-L1 testing but indeterminate will be considered to have prostate cancer that is non-PD-L1 positive.

The newly obtained biopsy tissue sample may be one that was obtained at any time prior to enrollment, as long as the subject has not received any intervening systemic therapy from the time the tissue was collected until the subject enrolls in the study.

Submission of FFPE tumor tissue 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.

Neither the archival tissue sample nor newly obtained biopsy (obtained ≤12 months prior to screening date) is required to have been obtained within 42 days of enrollment. Subjects must sign the main study consent prior to submitting existing tissue samples and/or undergoing a new biopsy.

Detailed instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

7.1.2.8 Tumor Marker Assessment (PSA)

The initial Prostate-Specific Antigen (PSA) biomarker assessment at screening must be performed within 28 days prior to the date of allocation/Cycle 1.

In the first year (through week 54), on study PSA biomarker assessments must be performed every 9 weeks (63 days ±7 days) from the date of allocation. After one year, subjects who remain on treatment will have PSA performed every 12 weeks (84 days ±7 days). PSA timing should follow calendar days from the date of allocation and should not be adjusted for delays in cycle starts.

In Cohorts 4 and 5, screening PSA by central results are required during the screening period as part of eligibility and should be drawn and sent to the central lab to ensure the result is available in time for allocation. PSA biomarker assessment must occur every 3 weeks (± 3 days) from the date of allocation/Cycle 1 while the subject is on trial treatment (at weeks 3 and 9) up to cycle 4 (week 12) then follow the imaging schedule as described above. PSA timing should follow calendar days from the date of allocation and should not be adjusted for delays in cycle starts.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by PSA biomarker assessments using the same schedule the subject was on during treatment (e.g. every 9 weeks [63 days ±7 days from the date of allocation] or every 12 weeks [84 days ±7 days from the date of allocation]) until: 1) the start of new anti-cancer treatment, 2) disease progression, 3) death or 4) the end of the study, whichever occurs first.

7.1.2.9 Patient Reported Outcomes (PROs)

The EQ-5D and FACT-P questionnaires should be completed electronically by subjects in the following order: EQ-5D first, then FACT-P. The questionnaires should be administered at Cycles 1, 2, 3, and 4 and every 3 cycles thereafter (Cycles 7, 10, 13, 16, and 19), at treatment discontinuation, and again 30 days after the last dose of trial treatment.

It is a best practice and strongly recommended that ePROs are administered to randomized subjects prior to drug administration, adverse event evaluation, and disease status notification. If the subject does not complete either of the ePRO questionnaires, the reason

the assessment was not performed must be captured in the appropriate study electronic case report form.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Platelet Count	Alanine Aminotransferase (ALT)	Protein	PT (INR)
WBC (Total and Differential)	Aspartate Aminotransferase (AST)	Specific Gravity	PTT / aPTT
Red Blood Cell Count	Lactate Dehydrogenase (LDH)	Microscopic Exam[b] *(If abnormal results are noted)*	Total Triiodothyronine (T3)[c]
Absolute Neutrophil Count	Carbon Dioxide[a] *(CO_2 or bicarbonate)*		Free Thyroxine (FT4)
Absolute Lymphocyte Count	Uric Acid		Thyroid Stimulating Hormone (TSH)
	Calcium		Blood for Genetic Analysis
	Chloride		Blood for Correlative Studies
	Glucose		Total Testosterone
	Phosphorus		Prostate-Specific Antigen (PSA)
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		

Hematology	Chemistry	Urinalysis	Other
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen (BUN) is preferred but Urea can be used if BUN not available		
	Creatinine[d]		
	Alkaline Phosphatase		
	Albumin		

a. If considered standard of care in your region.
b. Institutional standards are acceptable.
c. Free T3 may be performed in place of Total T3 per local standards
d. GFR (measured or calculated) or CrCl can be used in place of creatinine.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment.

After Cycle 1, pre-dose laboratory procedures may be conducted up to 72 hours prior to dosing. Results of scheduled laboratory tests must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Any results found to be clinically unacceptable may be repeated.

There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function test (T3, FT4, and TSH) results after dosing is acceptable.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of ADAs and PK are currently planned as shown in the Trial Flowchart (Section 6.1) for Cohorts 1 to 3 only. Blood samples for PK and ADA collected may be stored at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.2.1 Blood Collection for Serum MK-3475

PK serum samples must be drawn within 24 hours before infusion at Cycles 1, 2, 4, 6 and 8.

Post-dose PK serum samples will be drawn within 30 minutes after the end of infusion at Cycles 1 and 8. Additional single PK samples should be drawn at the following time points

after Cycle 1: 24 hours (±4 hours) [Day 2], between 72 and 168 hours [Day 4-8], and 336 hours (±48 hours) [Day 15].

Sample collection, storage and shipment instructions will be in the Procedures Manual.

7.1.3.2.2 Blood Collection for Anti-pembrolizumab Antibodies

Pre-dose anti-pembrolizumab antibody (ADA) samples must be drawn at the same time points as the pre-dose PK serum samples, as simultaneous PK sampling is required for interpretation of ADA analysis.

Sample collection, storage and shipment instructions will be in the Procedures Manual.

7.1.3.2.3 Blood Collection for RNA Analyses/Plasma and Serum Biomarker Analyses

Blood for RNA analyses, blood for plasma biomarker analyses and blood for serum biomarker analyses must be collected pre-dose at Cycles 1, 2, and 5 and at treatment discontinuation. Leftover samples may be kept for future biomedical research if the subject signs the FBR consent.

Sample collection, storage and shipment instructions will be in the Procedures Manual.

7.1.3.2.4 Blood Collection for CTC

Blood for CTC will be collected at Cycle 1 and at treatment discontinuation. Leftover samples may be kept for future biomedical research if the subject signs the FBR consent.

Sample collection, storage and shipment instructions will be in the Procedures Manual.

7.1.3.2.5 Blood Collection for ctDNA

Blood for ctDNA will be collected at Cycle 1, pre-infusion (if the collection coincides with a treatment cycle) every 9 weeks for the first year (through week 54) (63 days ±7 days), every 12 weeks in the second year, and at treatment discontinuation. The timing of these assessments should not be adjusted for dose delays or cycle starts. Leftover samples may be kept for future biomedical research if the subject signs the FBR consent.

Sample collection, storage and shipment instructions will be in the Procedures Manual.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual.

7.1.3.4 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

DNA for future research.

- Leftover archival tumor tissue or leftover newly obtained biopsy sample
- Leftover RNA
- Leftover Plasma and Serum from biomarker analyses
- Leftover Blood for CTC and Blood for ctDNA
- Leftover Blood for AR-V7

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End-of-Treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment- as required for inclusion labs and trial assessments
- Imaging equipment- as required for trial objectives
- Infusion equipment- as required for administering drug product.

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Pharmacy Manual and Site Imaging Manual.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 42 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

After providing main study consent subjects will be assigned a screening number. Subjects must sign the main study consent prior to submitting existing tissue samples and/or undergoing a new biopsy. Requirements pertaining to submission of tissue samples are found in Section 7.1.2.7.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 42 days prior to the first dose of trial treatment. The following procedures need to be performed within the specified time frames:

- Laboratory tests within 10 days prior to the first dose of trial treatment (unless otherwise noted in the protocol).
- ECOG within 10 days prior to the date of treatment allocation.
- Baseline imaging assessments by CT (or MRI) and bone scan within 28 days prior to the first dose of trial treatment.
- Prostate-Specific Antigen (PSA) tumor marker assessment within 28 days prior to the date of allocation.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

The subject identification card will be updated with the screening number.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab (MK-3475) with SD or better may be eligible for up to 17 additional infusions of pembrolizumab (MK-3475) therapy if they progress after stopping MK-3475. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Either
    - Stopped initial treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
        - Was treated for at least 8 administrations with pembrolizumab (MK-3475) before discontinuing therapy
        - Received at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared

      OR

    - Subject had SD, PR or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of pembrolizumab (MK-3475) treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab (MK-3475)
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab (MK-3475)
- Has a performance status of 0, 1, or 2 on the ECOG Performance Scale
- Demonstrate adequate organ function as detailed in Section 5.1.2
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab (MK-3475). Treatment will be administered for up to 17 additional administrations of pembrolizumab (approximately one year).

Visit requirements are outlined in Section 6.1 – Trial Flow Chart.

7.1.5.3 Post-Treatment

Subjects will be required to return to clinic approximately 30 days after the last dose of trial drug for the post-treatment visit. If the post-treatment visit occurs less than 30 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 30 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit.

7.1.5.3.1 Survival Follow-up

Subjects who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to an efficacy interim analysis and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation 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 unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization 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, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab defined as any dose greater than 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization 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, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. 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 events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;

- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: 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 to meet certain local requirements. Therefore, these 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.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, 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 (reference Section 7.2.3.3 for additional details), 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization 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 (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product 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.

7.2.3.2 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 allocation/randomization, 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate PK analysis plan, as well as biomarker analysis plan, will be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.11.

Study Design Overview	Phase II Trial of Pembrolizumab (MK-3475) in Subjects with mCRPC
Treatment Assignment	This is a single-arm, open-label study. All subjects will receive pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W).
Analysis Populations	Efficacy: The All Subjects as Treated (ASaT) population will serve as the primary population for the analysis of efficacy data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment. The analysis population for ORR consists of all subjects with measurable disease at baseline in ASaT. Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Cohorts 1, 2, and 4: Objective response rate (ORR) per RECIST 1.1 assessed by central imaging vendor
Secondary Endpoints	Duration of response (DOR) per RECIST 1.1 and PCWG3-modified RECIST 1.1, disease control rate (DCR), radiographic progression-free survival (rPFS) where progressive disease (PD) in bone metastases will be determined by radionuclide bone scan using PCWG3 criteria and PD for all other tumors will be determined using by RECIST 1.1 by central imaging vendor, PSA response rate, time to PSA progression, overall survival (OS) Cohorts 4 and 5 only: duration of PSA response, time to initiation of cytotoxic chemotherapy, time to new-anticancer therapy, time to first skeletal-related event

Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	For ORR: the point estimate and 95% CI will be calculated using an exact method based on binomial distribution (Clopper-Pearson method)
Statistical Methods for Key Safety Analyses	Count and percentage of AEs will be provided.
Interim Analyses	The interim analysis is summarized below. Details are provided in Section 8.7. • Timing: To be performed about 27 weeks after the first 100 subjects with RECIST 1.1-measurable disease (Cohorts 1 and 2) and all subjects in Cohort 3 have been enrolled. • Scope of analyses: ORR, DOR and safety will be evaluated
Multiplicity	There will be no hypothesis testing performed in this study. For the primary and secondary objectives in this Phase II study, no adjustment to control for Type I error is planned.
Sample Size and Power	The planned sample size is approximately 370 including: Cohorts 1-3: subjects with mCRPC previously treated with docetaxel-based chemotherapy; Cohort 1 includes subjects with PD-L1 positive, RECIST 1.1-measurable disease and Cohort 2 includes subjects with PD-L1 negative, RECIST 1.1-measurable disease (n≈200 in Cohorts 1 and 2 combined); Cohort 3 includes subjects with bone-metastases, RECIST 1.1 non-measurable (n≈50) Cohorts 4 and 5: subjects who are on pre-chemotherapy enzalutamide treatment and failing or showing early signs of failing enzalutamide treatment Cohort 4: subjects with RECISIT 1.1-measurable disease (n≈80) Cohort 5: subjects bone metastases only or bone-predominant disease, RECIST 1.1 non-measurable (n≈40)

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This is an open-label trial; therefore, the Sponsor, investigators, and subjects will know the treatment administered.

Association between biomarker status and clinical response/resistance will be explored. The subjects-level biomarker results will be masked in the database to the study team, including clinical, statistical, statistical programming, and data management personnel throughout the study period until database lock for the primary study report. Access to the biomarker subject-level results will be limited to an unblinded Sponsor clinical scientist, unblinded Sponsor data management personnel, unblinded Sponsor statistician, and unblinded Sponsor statistical programmer who will be responsible for biomarker data review and analysis. Analyses related to biomarker scores will be conducted by a sponsor unblinded statistician. Unblinded analyses related to biomarker scores will be limited to biomarker score vs outcome at the interim analysis and conducted by a sponsor unblinded biomarker statistician.

8.3 Hypotheses/Estimation

This trial is being conducted as an open-label study. There is no randomization in the study. Objectives and associated estimations of the study are stated in Section 3.

8.4 Analysis Endpoints

8.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Primary

- **Objective Response Rate (ORR) – per RECIST 1.1 assessed by central imaging vendor**

Proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) where responses are determined by RECIST 1.1 assessed by central imaging vendor.

Secondary

- **Duration of Response (DOR) – per PCWG3-modified RECIST 1.1 assessed by central imaging vendor**

For subjects who demonstrated CR or PR, DOR is defined as the time from first documented evidence of CR or PR until progressive disease (PD) assessed by central imaging where PD will be determined by radionuclide bone scan using RECIST 1.1/PCWG3 criteria and PD for all other tumors will be determined using RECIST 1.1 or death due to any cause, whichever occurs first.

- **Duration of Response (DOR) – per RECIST 1.1 assessed by central imaging vendor**

For subjects who demonstrated CR or PR, DOR is defined as the time from first documented evidence of CR or PR until progressive disease (PD) assessed by central imaging using RECIST 1.1 or death due to any cause, whichever occurs first.

- **Disease Control Rate (DCR) – per PCWG3-modified RECIST 1.1 assessed by central imaging vendor**

Proportion of subjects in the analysis population who have CR or PR or stable disease (SD) for at least 6 months, by central imaging vendor where PD in bone-only tumors will be determined by radionuclide bone scan using PCWG3 criteria and PD for all other tumors will be determined using RECIST 1.1.

- **PSA Response Rate**

Proportion of subjects in the analysis population who have PSA response defined as at least 50% decline from baseline measured twice at least 3 weeks apart.

- **Time to PSA Progression**

Time to PSA progression is defined as the time from first day of study treatment to the date of PSA progression. Subjects without PSA progression will be censored at the last PSA assessment date. PSA progression is defined as the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir are documented. For subjects who have a decline in PSA during treatment, PSA progression must be confirmed by a second value 3 or more weeks later increased with respect to the nadir PSA.

- **Radiographic progression-free survival (rPFS) – per PCWG3-modified RECIST 1.1 assessed by central imaging vendor**

Progression-free-survival (rPFS) is defined as the time from first day of study treatment to the documented disease progression by central imaging vendor where PD in bone-only tumors will be determined by radionuclide bone scan using PCWG3 criteria and PD for all other tumors will be determined using RECIST 1.1 or death due to any cause, whichever occurs first.

- **Overall Survival (OS)**

Overall survival (OS) is defined as the time from first day of study treatment to the time of death.

- **Duration of PSA response (Cohorts 4 and 5 only)**

Duration of PSA response is defined as the time from PSA response, when the PSA value first declines by at least 50% of the baseline (must be confirmed by a second value), to the date of PSA progression at which there is an increase of 25% or more from the nadir PSA, provided the absolute increase from the nadir PDA is at least 2 ng/mL.

- **Time to initiation of cytotoxic chemotherapy (Cohorts 4 and 5 only)**

Time to initiation of cytotoxic chemotherapy is defined as the time from first day of study treatment to the time of initiation of cytotoxic chemotherapy for prostate cancer.

- **Time to new-anticancer therapy (Cohorts 4 and 5 only)**

Time to new-anticancer therapy is defined as the time from first day of study treatment to the time of new-anticancer therapy for prostate cancer

- **Time to first skeletal-related event (Cohorts 4 and 5 only)**

Time to initiation of first skeletal-related event is defined as the time from first day of study treatment to the first skeletal-related event, which is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change or antineoplastic therapy to treat bone pain. See Section 8.6.1 for censoring rules.

8.4.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with mCRPC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to study treatment, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

8.5 Analysis Populations

Subjects will be entered into the trial when they are assigned an allocation number by the IVRS/IWRS.

8.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will serve as the primary population for the analysis of efficacy data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

The analysis of DCR, PSA response rate, time to PSA progression, time to initiation of cytotoxic chemotherapy, time to new-anticancer therapy, time to first skeletal-related event, rPFS, and OS will be based on the ASaT population.

The analysis of ORR will be based on all subjects with measurable disease at baseline in the ASaT population.

The analysis of DOR will be based on all responders with measurable disease at baseline in the ASaT population.

The analysis of duration of PSA response will be based on all PSA responders with at least 50% decline from baseline measured twice at least 3 weeks apart. The primary analysis will comprise all subjects with measurable PSA at baseline; the secondary analysis will comprise all subjects with elevated PSA at baseline as a sensitivity analysis.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.5.3 Biomarker Discovery Population

The biomarker discovery population consists of the first 100 subjects with RECIST1.1-measurable disease in Cohorts 1 and 2 who are clinically evaluable, which is defined as any subjects who received at least one dose of study drug and had at least 3 post-baseline scans, or discontinued due to radiographic/clinical progression or death before reaching Week 27.

The biomarker discovery population will be used in this study for the evaluation of the association between biomarker score and clinical efficacy and subsequently to determine a biomarker cut-point (if applicable and necessary). The biomarker discovery population will be excluded from any subsequent validation analyses for any biomarker selected population, if applicable. These subjects will still be included in the general efficacy analyses for combined cohorts and by each cohort irrespective of biomarker status.

8.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.6.2. In addition, separate SAPs will describe the analysis of Pharmacokinetic (PK) data described in Section 7.1.3.2 and a biomarker analysis plan.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

For ORR, DCR and PSA response rate, the point estimate and 95% confidence interval will be provided using the exact binomial method proposed by Clopper and Pearson (1934). Subjects in the analysis population without response data will be counted as non-responder.

For rPFS, DOR, time to PSA progression, duration of PSA response, time to initiation of cytotoxic chemotherapy, time to new-anticancer therapy, time to first skeletal-related event, and OS, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

Censoring rules for DOR are summarized in Table 8.

Table 8 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 missed adequate disease assessments	Last adequate disease assessment prior to the after ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	PD or death	End of response (Event)
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up		

Table 9 summarizes the key efficacy analyses.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
ORR per RECIST 1.1 assessed by central imaging vendor	Exact method based on binomial distribution (Clopper-Pearson method)	Subjects with measurable disease at baseline in ASaT in all below populations • Cohorts 1 and 2 • Cohort 1 • Cohort 2 • Cohort 4	Subjects with missing data are considered non-responders
DOR per RECSIT 1.1 and per PCWG3-modified RECIST 1.1 assessed by central imaging vendor	Summary statistics using Kaplan-Meier method	Responders with measurable disease at baseline in ASaT in all below populations • Cohorts 1 and 2 • Cohort 1 • Cohort 2 • Cohort 4	Details are provided in a separate table

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
DCR per PCWG3-modified RECIST 1.1 assessed by central imaging vendor	Exact method based on binomial distribution (Clopper-Pearson method)	ASaT • Cohorts 1+2+3 • Cohorts 1+2 • Cohorts 4+5 • Each Cohort	Subjects with missing data are considered disease not under control
PSA Response Rate	Exact method based on binomial distribution (Clopper-Pearson method)	ASaT • Cohorts 1+2+3 • Cohorts 1+2 • Cohorts 4+5 • Each Cohort	Subjects with missing data are considered non-responders
Time to PSA Progression	Summary statistic using Kaplan-Meier method	ASaT • Cohorts 1+2+3 • Cohorts 1+2 • Cohorts 4+5 • Each Cohort	Censored at last assessment date
Radiographic PFS per PCWG3-modified RECIST 1.1 assessed by central imaging vendor	Summary statistics using Kaplan-Meier method	ASaT • Cohorts 1+2+3 • Cohorts 1+2 • Cohorts 4+5 • Each Cohort	Censored at last assessment date
OS	Summary statistics using Kaplan-Meier method	ASaT • Cohorts 1+2+3 • Cohorts 1+2 • Cohorts 4+5 • Each Cohort	Censored at last date known alive
Duration of PSA response	Summary statistics using Kaplan-Meier method	PSA responders in • Cohorts 4 and 5 • Cohort 4 • Cohort 5	Censored at last assessment date if no new anti-cancer therapy initiated or last adequate disease assessment before new anti-cancer therapy initiated

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Time to initiation of cytotoxic chemotherapy	Summary statistics using Kaplan-Meier method	ASaT in • Cohorts 4 and 5 • Cohort 4 • Cohort 5	Censored at last date known alive
Time to new-anticancer therapy	Summary statistics using Kaplan-Meier method	ASaT in • Cohorts 4 and 5 • Cohort 4 • Cohort 5	Censored at last date known alive
Time to first skeletal-related event	Summary statistics using Kaplan-Meier method	ASaT in • Cohorts 4 and 5 • Cohort 4 • Cohort 5	Censored at last date known alive

8.6.2 Statistical Methods for Safety Analyses

Safety will be summarized for the overall safety population for Cohorts 1, 2, and 3 in the post-chemotherapy population and overall safety for Cohorts 4 and 5 in the pre-chemotherapy population. If there is no difference among individual patient populations, an overall analysis will be performed.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Count and percentage of AE will be provided.

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The summary statistics of count and percentage will be provided for the incidence rate of any AE, any serious AE, any Grade 3-5 AE, any drug-related AE, any serious and drug-related AE, any Grade 3-5 and drug-related AE, dose interrupted due to AE, discontinuation due to AE, any immune-related AE (irAE), death and specific AEs.

The summary statistics of mean and standard deviation will be provided for change from Baseline Results (Labs and Vital Signs) within each treatment cycle. The summary statistics of count and percentage will be provided for laboratory worsening from Baseline in terms of CTCAE grades.

8.6.3 Statistical Methods for Biomarker Analyses

The evaluation of a general positive association between biomarker score and ORR/DCR will be investigated via standard logistic regression as well as generalized additive models. The profiles of PPV (positive predictive value), NPV (negative predictive value), and the percentage of subjects above a given cut-off, along with intervals quantifying the uncertainty in those profiles, will be estimated as a function of potential cut-offs. A biomarker cut-off that maintains high NPV (e.g., near or above 90%) while achieving meaningful enrichment of response and largely capturing subjects showing durable clinical benefit is sought. Receiver operating characteristic curve analysis will also be used to understand the sensitivity and specificity profile and examine cut-offs that might be suggested based on the ROC curve and their appropriateness with regard to PPV and NPV.

8.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analysis

Efficacy and safety data will be monitored over time in this single-arm, open-label, multi-cohort study.

One interim analysis will be conducted in the first 100 subjects with RECIST 1.1-measurable disease by RECIST 1.1 (Cohort 1 and Cohort 2) and all subjects in Cohort 3 at about 27 weeks after the completion of enrollment of all these subjects. Other analyses at the interim analysis will include DOR and safety.

A biomarker analysis is planned at the time of the interim analysis where a subset of subjects (the biomarker discovery population, about 100 subjects from Cohorts 1 and 2, see Section 8.5.3 for details) will be used to explore the association between the biomarker score and clinical efficacy/resistance and also to determine the biomarker cut-point. More subjects may be allocated to the biomarker discovery population, if necessary.

The final analysis of ORR in the population with measurable disease by RECIST 1.1 will be performed after all subjects have been enrolled and all subjects have accumulated mature data and had adequate follow-up. All other analyses, including safety, DOR, DCR, PSA response, time to PSA progression, rPFS, and OS will be analyzed at this time.

8.8 Multiplicity

There will be no hypothesis testing performed in this study. For the primary and secondary objectives in this Phase II study, no adjustment to control for Type I error is planned.

8.9 Sample Size and Power Calculations

The primary objective of this study is to estimate ORR in Cohorts 1 and 2 combined, Cohort 1, Cohort 2, and Cohort 4. The planned sample size is approximately 370 with about 200 subjects in Cohorts 1 and 2, 50 subjects in Cohort 3, 80 subjects in Cohort 4, and 40 subjects in Cohort 5. With a sample size of 200, 100, and 80, the confidence intervals for an observed response rate of 10%, 15%, 20%, 25% and 30% are listed below for 95% confidence level (Table 10). In addition, about 50 subjects with bone-predominant disease at baseline for Cohort 3 will be enrolled.

Table 10 Confidence Intervals for Different Observed Response Rates and Sample Size

Sample Size	Number of Subjects with a response	Observed Response Rate	95% CI	95% CI Width
200	20	10%	(6.2%, 15.0%)	8.8%
200	30	15%	(10.4%, 20.7%)	10.4%
200	40	20%	(14.7%, 26.2%)	11.5%
200	50	25%	(19.2%, 31.6%)	12.4%
200	60	30%	(23.7%, 36.9%)	13.1%
100	10	10%	(4.9%, 17.6%)	12.7%
100	15	15%	(8.6%, 23.5%)	14.9%
100	20	20%	(12.7%, 29.2%)	16.5%
100	25	25%	(16.9%, 34.7%)	17.8%
100	30	30%	(21.2%, 40.0%)	18.7%
80	8	10%	(4.4%, 18.8 %)	14.3%
80	12	15%	(8.0%, 24.7 %)	16.7%
80	16	20%	(11.9%, 30.4 %)	18.6%
80	20	25%	(16.0%, 35.9 %)	19.9%
80	24	30%	(20.3%, 41.3 %)	21.0%

8.10 Subgroup Analyses and Effect of Baseline Factors

For the primary objective ORR, subgroup analyses to be performed include but may not be limited to following subgroups based on

- Age (<65 years, ≥65 years)
- Race
- PD-L1 expression level (positive, negative),
- And biomarker status as appropriate
- RECIST-measurability (yes, no)

Categories of subgroup may be subject to change according to actual data. Categories with few than 5 subjects might not be considered or might be combined into other categories.

8.11 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 11.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 11 Product Description

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 50 mg	Lyophilized powder for IV infusion	Provided centrally by the Sponsor.
Pembrolizumab (MK-3475) 100 mg/4 mL (25 mg/mL)	Solution for IV infusion	Provided centrally by the Sponsor

All supplies indicated in Table 11 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 11 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label pembrolizumab (MK-3475), supplied either as vials containing 50 mg of lyophilized powder, or as kits containing 2 vials of solution for infusion.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by

the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol,

the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees

to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms

signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

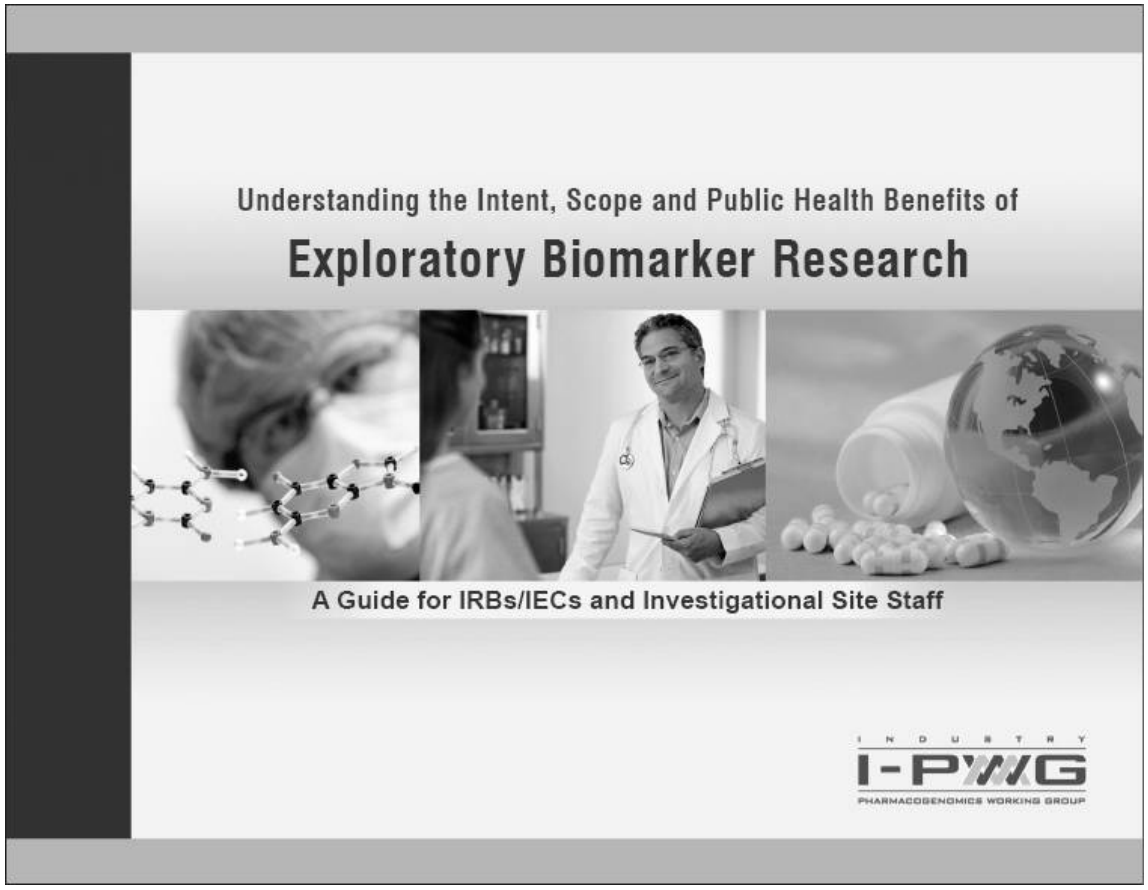
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

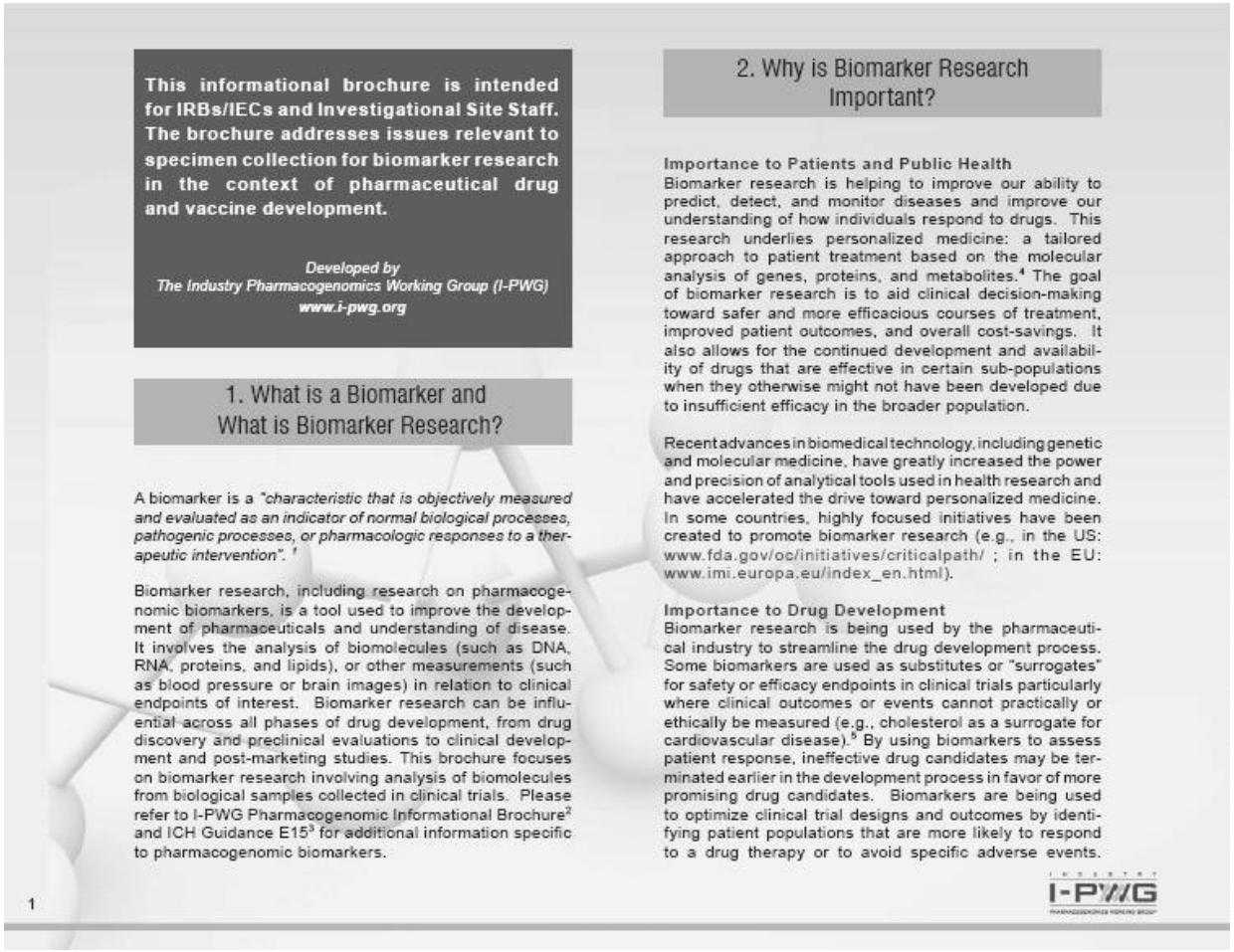
13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

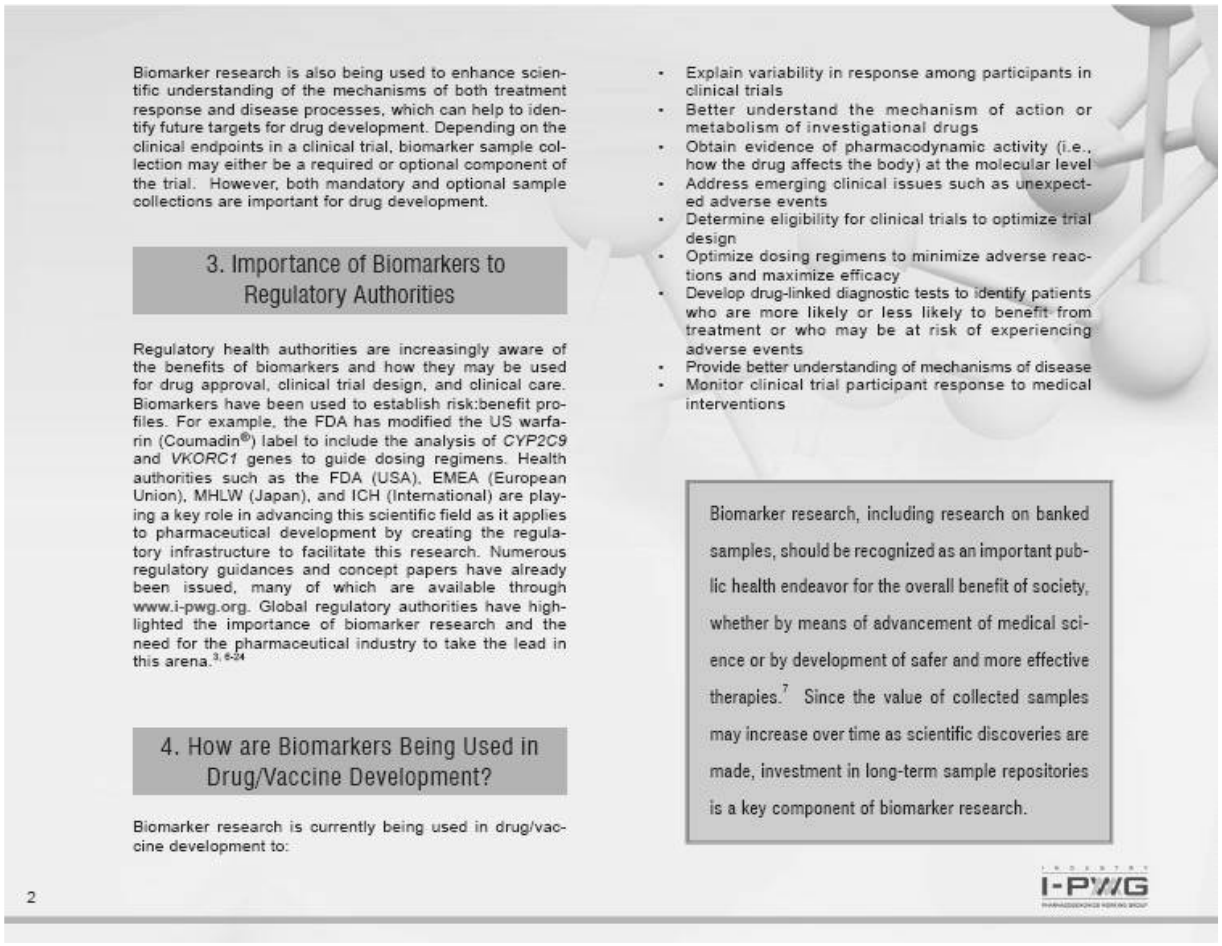
Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

1

I-PWG



Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

2

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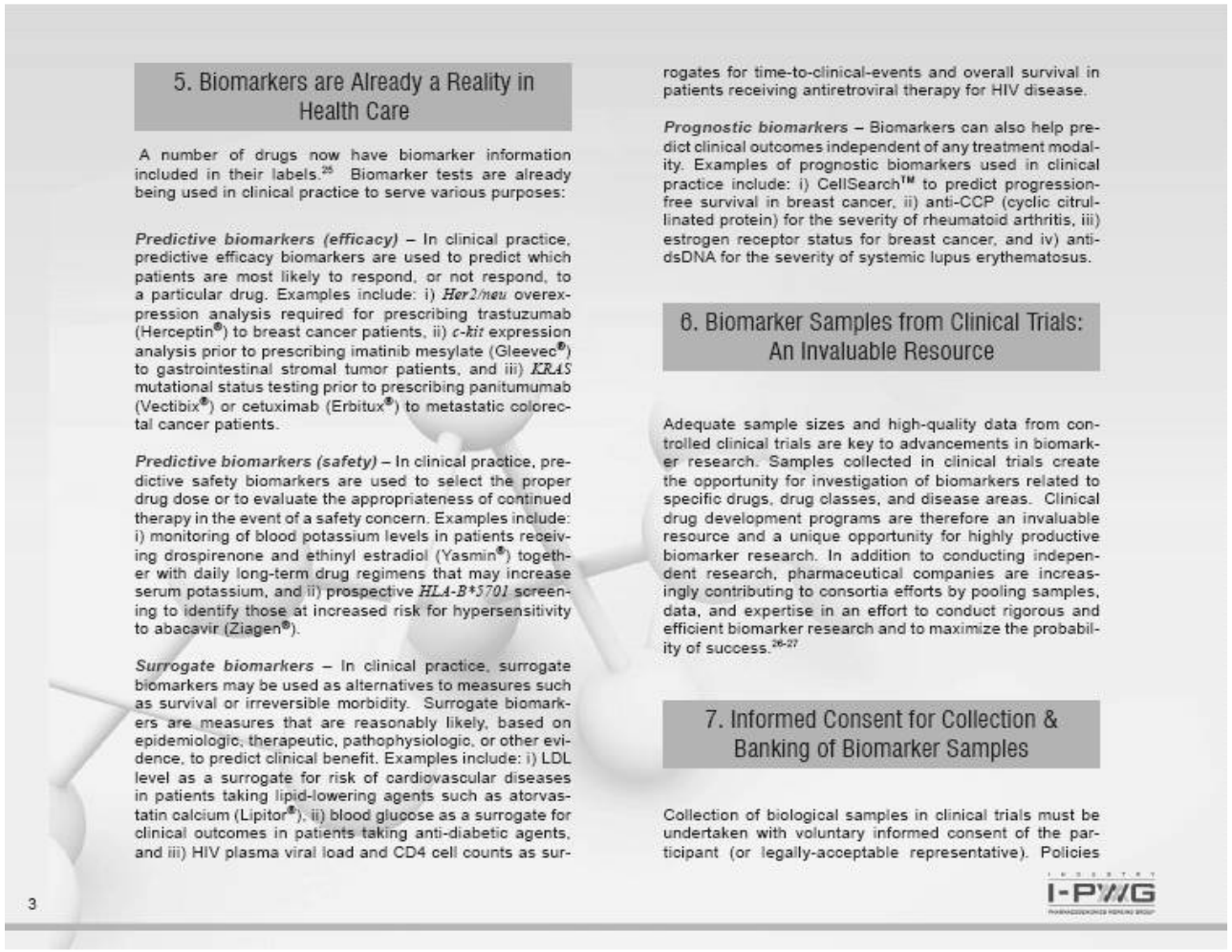


5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

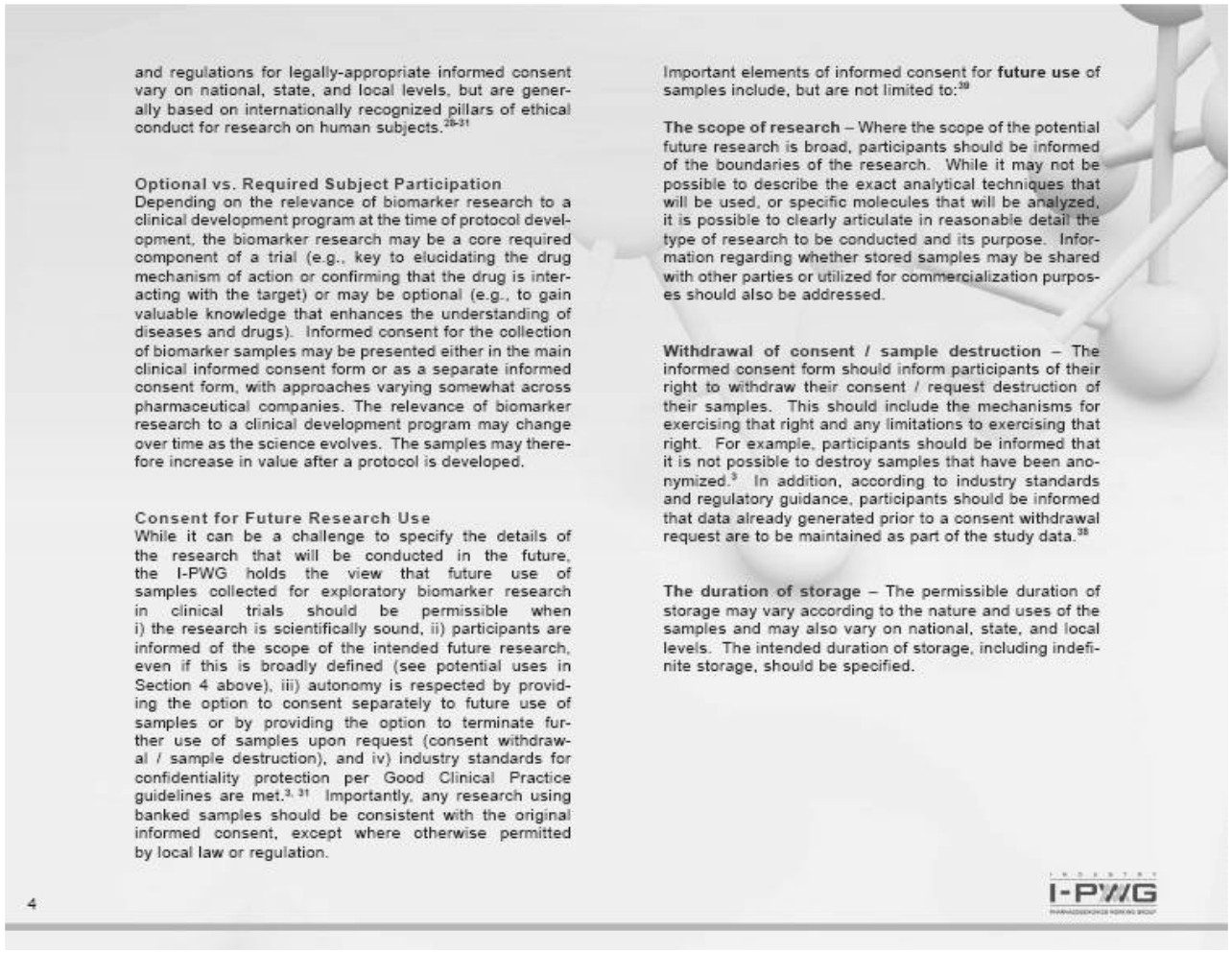
Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

3

I-PWG



and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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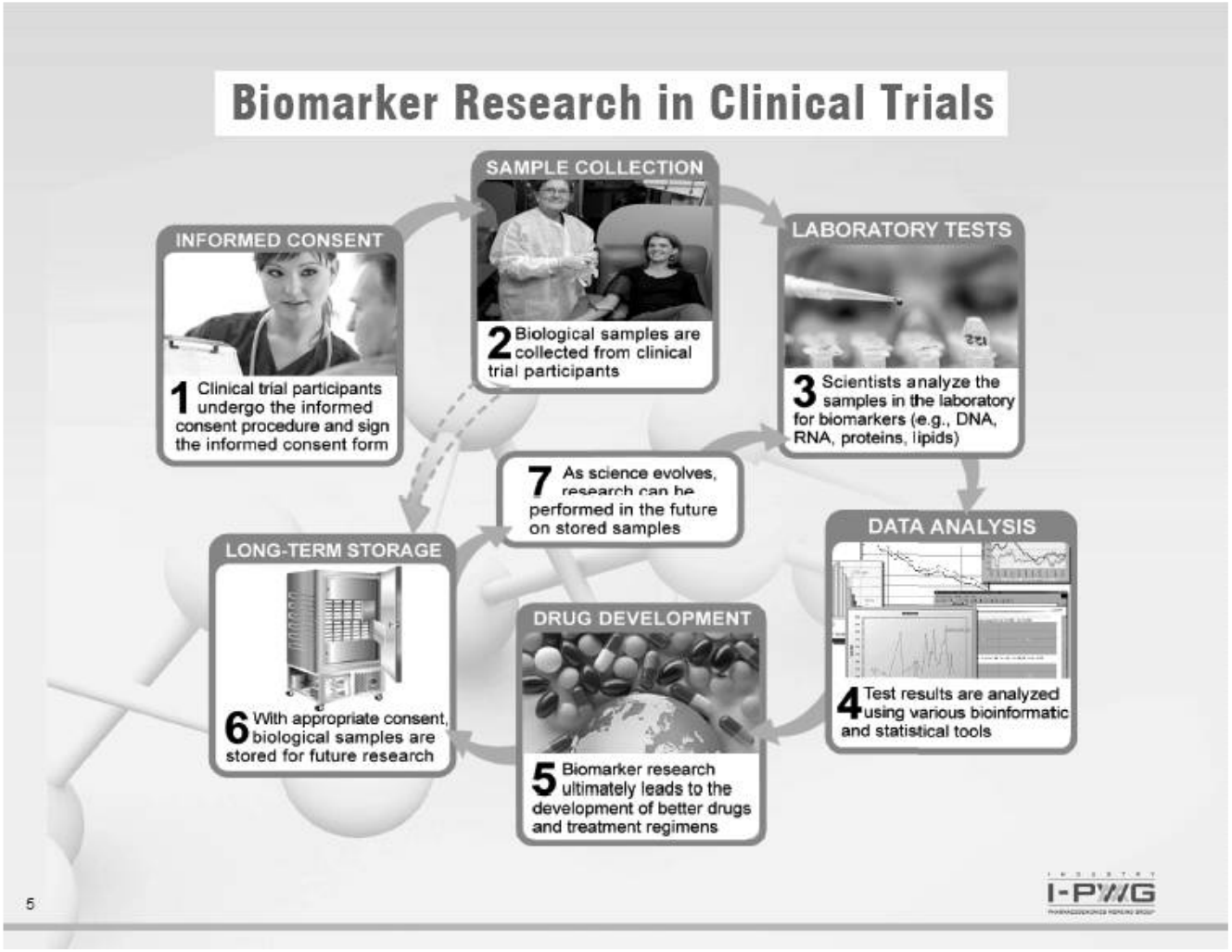
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
5
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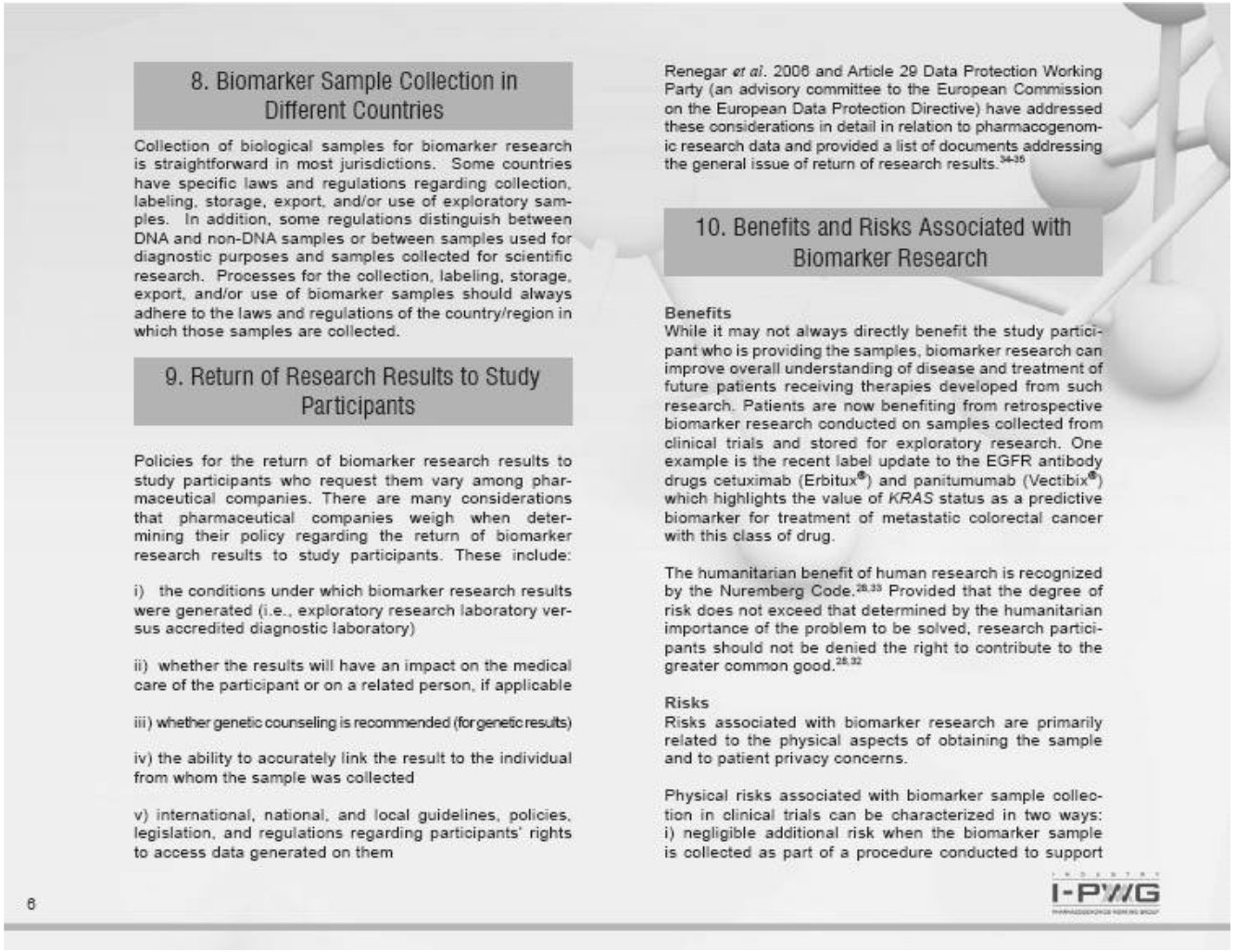

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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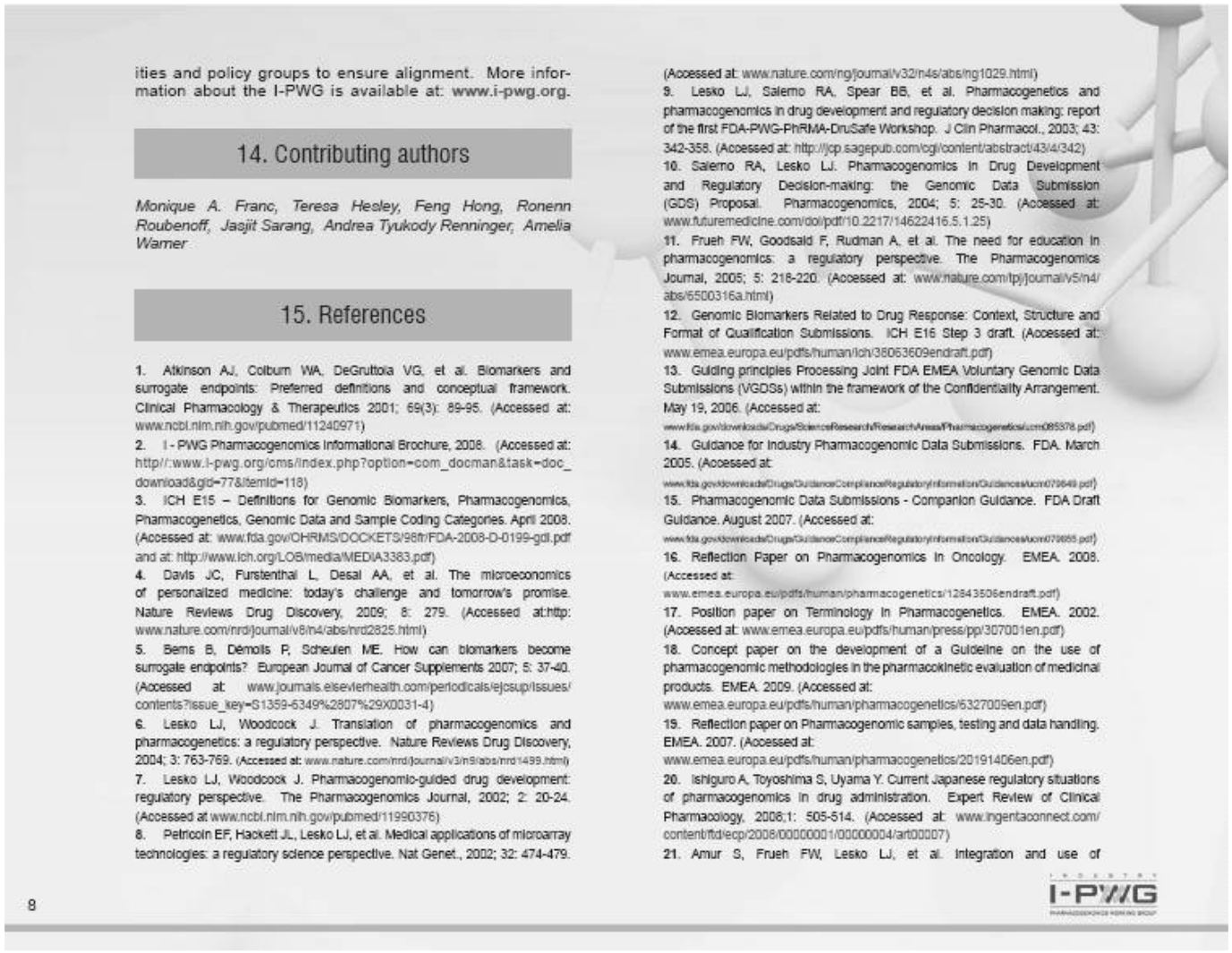

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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I-PWG


www.i-pwg.org

12.4 List of Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
ADA	Anti-Drug Antibodies
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
ADT	Androgen deprivation therapy
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AR-V7	Androgen-receptor isoform encoded by splice variant 7
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
BCG	Bacillus-Calmette Guerin (vaccine)
BOR	Best Overall Response
C1D1	Cycle 1 day 1
C_{max}	Maximum concentration
C_{trough}	Minimum concentration
CAC	Clinical Adjudication Committee
CBC	Complete Blood Count
CDC	Complement-dependent Cytotoxicity
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical trial assay
CTC	circulating tumor cell assay
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
dL	Deciliter
DCR	Disease Control Rate
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
EBMT	European Group for Blood and Marrow Transplantation
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunoassay
ERC	Ethics Review Committee
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation/Term	Definition
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin fixed and paraffin embedded
FSH	Follicle Stimulating Hormone
g	Gram
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage - Colony Stimulating Factor
HCB	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
hr	Hour
HRQOL	health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
irRECIST	immune-related RECIST
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
IVRS	Integrated Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
LDH	Lactate Dehydrogenase
LHRH	Luteinizing-Hormone-Releasing Hormone
LOCF	Last Observation Carried Forward
mAb	Monoclonal antibody
mCRPC	Metastatic Castration-resistant Prostate Cancer
mcL	Microliters
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melanoma
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	Microsatellite instability
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NK	Natural Killer
NPV	Negative predictive value
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-Counter
PCWG3	Prostate Cancer Working Group

Abbreviation/Term	Definition
PD	Progressive Disease
PD-1	Programmed Cell Death 1 Receptor
PD-L1	Programmed Cell Death Ligand 1 Receptor
PD-L2	Programmed Cell Death Ligand 2 Receptor
PFS	Progression Free Survival
PI	Principal Investigator
PIN	Personal Identification Number
PK	Pharmacokinetic
PO	Oral Administration
PPV	Positive predictive value
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PSA	Prostate-specific Antigen
PT	Prothrombin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QALY	Quality-adjusted life-years
QoL	Quality of Life
RNA	Ribonucleic Acid
rPFS	Radiographic Progression Free Survival
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
T3	Total Thyroidothyronine
T4	Free Tyroxine
TIL	Tumor Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
V	Volume
Variable-type	V-type
WBC	White Blood Cell
WOCBP	Woman/women of childbearing potential

12.5 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

12.6 Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

(http://ctep.cancer.gov/reporting/ctc.html).

12.7 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer [41].

12.8 Contraceptive Guidance

Definition

Women of Childbearing Potential (WOCBP) Nonparticipant Only

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

- Women in the following categories are not considered WOCBP:
  - Premenarchal
  - Premenopausal female with 1 of the following:
    - Hysterectomy
    - Bilateral salpingectomy
    - Bilateral oophorectomy
    - Permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity.
    - Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	