Official Protocol Title:	A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)
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TITLE:

A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)

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DOCUMENT HISTORY

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2.1	[redacted]		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

[redacted]

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase III Study of Pembrolizumab (MK-3475) vs Chemotherapy in Microsatellite Instability-High or Mismatch Repair Deficient Stage IV Colorectal Carcinoma
Trial Phase	Phase III
Clinical Indication	Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Carcinoma
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	• Arm 1: Pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W) OR • Arm 2: Standard of Care (SOC): Investigator's choice of the following: o mFOLFOX6, or o mFOLFOX6 + bevacizumab, or o mFOLFOX6+ cetuximab, or o FOLFIRI, or o FOLFIRI+ bevacizumab, or o FOLFIRI+ cetuximab
Number of trial subjects	Approximately 300 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 65 months [redacted]) 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 study 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 can be randomized to either pembrolizumab (experimental arm) or standard of care chemotherapy (control arm). Subjects will receive pembrolizumab (MK-3475) beginning on Day 1 of each 3-week dosing cycle or chemotherapy beginning on Day 1 of each 2-week cycle. The chemotherapy to be used must be chosen before randomization. Subjects will be randomized in a 1:1 fashion to standard chemotherapy per Investigator's choice or to pembrolizumab (MK-3475). Treatment on study will continue until progressive disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevents further administration of study medication, Investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, noncompliance with study medication or procedure requirements, administrative reasons, or the subject had received 35 treatments (approximately 2 years; pembrolizumab arm only) (see Section 5.8). Subjects who stop pembrolizumab (MK-3475) as a result of obtaining a locally confirmed complete response (CR), or after receiving 35 treatments (approximately. 2 years) and have stable disease (SD) or

	better may be eligible, at the discretion of the Investigator, for an additional 17 treatments (approximately 1 year) after experiencing PD while off pembrolizumab (MK-3475) if they meet the criteria for re-treatment; this will be designated the Second Course Treatment Phase (see Section 7.1.6.3 for details). Subjects randomized to the chemotherapy arm will have the option to crossover and receive 35 treatments with pembrolizumab (MK-3475) in the Crossover Phase (approximately 2 years) after verification of PD by a blinded independent central imaging vendor per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (see Section 7.1.4.5 for details). Subjects who stop pembrolizumab (MK-3475) in the crossover phase as a result of obtaining a locally confirmed CR, or after receiving 35 treatments (approximately 2 years) and have SD or better may be eligible, at the discretion of the Investigator, for an additional 17 treatments (approximately 1 year) in the Second Course Treatment Phase after experiencing PD while off pembrolizumab (MK-3475) if they meet the criteria for re-treatment (see Section 7.1.6.3 for details). After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAE) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects will have post-treatment follow-up for disease status, until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to 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 9 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. During the study, subjects may undergo resection of the primary tumor and metastasectomy with curative intent if deemed eligible per site institutional standard after achieving a response to study medication.
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.7.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a two-arm, multicenter, international, randomized, open-label, controlled study of pembrolizumab (MK-3475) monotherapy versus standard chemotherapy in subjects who have stage IV Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) colorectal carcinoma (CRC). MSI, a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers (Refer to Section 4.2.4.4 for further details). Subjects will be required to have at least 1 measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for response assessment. Subjects will be randomized in a 1:1 ratio to receive pembrolizumab (experimental arm) or the Investigator's choice of standard of care (SOC) chemotherapy (control arm). The chemotherapy to be used must be chosen before randomization.

Pembrolizumab (MK-3475) arm subjects will receive up to 35 administrations of pembrolizumab (approximately 2 years) in the Initial Treatment Phase. Subjects who stop pembrolizumab (MK-3475) with locally confirmed complete response (CR), or stable disease (SD) or better at the end of the Initial Treatment Phase may be treated in a Second Course Treatment Phase with up to 17 administrations of pembrolizumab (MK-3475) if they meet criteria outlined in Section 7.1.6.3.

Control arm subjects with progressive disease (PD) per RECIST 1.1 as verified by a blinded independent central imaging vendor who meet all crossover criteria will have an option to receive pembrolizumab (MK-3475) in the Crossover Phase. See Section 7.1.6.4 for crossover criteria and guidance. This may be followed by 17 additional treatments in the Second Course Treatment Phase if criteria as outlined in section 7.1.6.3 are met.

The primary objectives of the study are progression-free survival (PFS) per RECIST 1.1 assessed by an independent central imaging vendor based on the first radiologic progressive disease (PD) from the primary treatment to which subjects are randomized and overall survival (OS). On-study imaging assessments, performed every 9 weeks (Q9W), will be calculated from the date of randomization and independent of treatment delays for both treatment arms. RECIST 1.1 will be used by the site for the treatment decisions until verification of initial site-assessed PD by the blinded independent central imaging vendor. For subjects receiving pembrolizumab (MK-3475), following verification of PD by the central imaging vendor, further treatment decisions may be made by the adaptation of RECIST 1.1 as described in Section 4.2.4.2.1 termed immune-related RECIST (irRECIST) to accommodate for the tumor response patterns seen with pembrolizumab (MK-3475) treatment (eg, tumor flare). For a clinically stable subject with first radiologic evidence of PD per RECIST 1.1 as verified by the central imaging vendor, per irRECIST, it is at the discretion of the site Investigator to continue treating the subject with pembrolizumab (MK-3475) until PD is confirmed at least 4 weeks from the date of first radiologic PD by RECIST 1.1. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment unless, in the opinion of the Investigator, the subject is achieving a clinically meaningful benefit, in which case an exception to continue treatment may be considered following consultation with the Sponsor (see Section 7.1.4.6). France only: If radiologic PD is confirmed by the subsequent tumor imaging, the subject must be discontinued from treatment.

Subjects will continue to be treated with study medication until PD, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, noncompliance with study medication or procedure requirements, administrative reasons, or the subject has received 35 treatments (approximately 2 years; pembrolizumab arm only).

Subjects may undergo resection of the primary tumor and metastasectomy with curative intent after achieving a response to study medication converting unresectable to resectable disease if deemed eligible per Investigator's discretion in a multidisciplinary approach according to his/her institutional standard. After surgery, subjects in the SOC arm may resume the same therapy that they were receiving pre-operatively when clinically

appropriate. For instance, only mFOLFOX6/Bevacizumab may be used post-operatively (at the investigator's discretion) if a subject was assigned to the FOLFOX/ Bevacizumab arm pre-operatively. The duration of post-operative therapy is at the investigator's discretion per institutional standard. Pembrolizumab (MK-3475) subjects may also resume therapy post-operatively, and receive up to 35 total treatments inclusive of both pre- and post-operative periods. Pembrolizumab subjects who progress post-operatively will have an option to receive pembrolizumab (MK-3475) in the Second Treatment Course Phase with up to 17 administrations (approximately 1 year) of pembrolizumab (MK-3475) if clinically appropriate. Subjects in the SOC arm who progress post-operatively may have an option to receive pembrolizumab (MK-3475) in the Crossover Phase with up to 35 administrations (approximately 2 years) of pembrolizumab (MK-3475), followed by 17 administrations of pembrolizumab (MK-3475) in the Second Treatment Course, also if clinically appropriate. Subjects from both arms of the study who develop isolated lesion/tumor growth in the setting of overall clinical benefit may resume the assigned therapy after completing local treatment for the isolated lesion/tumor growth provided there is mutual agreement between the Investigator and Sponsor.

Subjects who receive pembrolizumab (MK-3475) and attain locally confirmed CR per RECIST 1.1 or irRECIST by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months) with pembrolizumab (MK-3475) may discontinue treatment at the discretion of the Investigator after receiving at least 2 treatments beyond the initial determination of a CR. Adverse events will be monitored throughout the study 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 (Section 12.6). Each subject will be monitored for AEs for 30 days after discontinuation of study medication. Serious adverse events (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.

All subjects (including subjects who have received the maximum 35 pembrolizumab treatments) will have post-treatment follow-up for disease status, until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to 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 9 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

This study will be conducted in conformance with Good Clinical Practices (GCP).

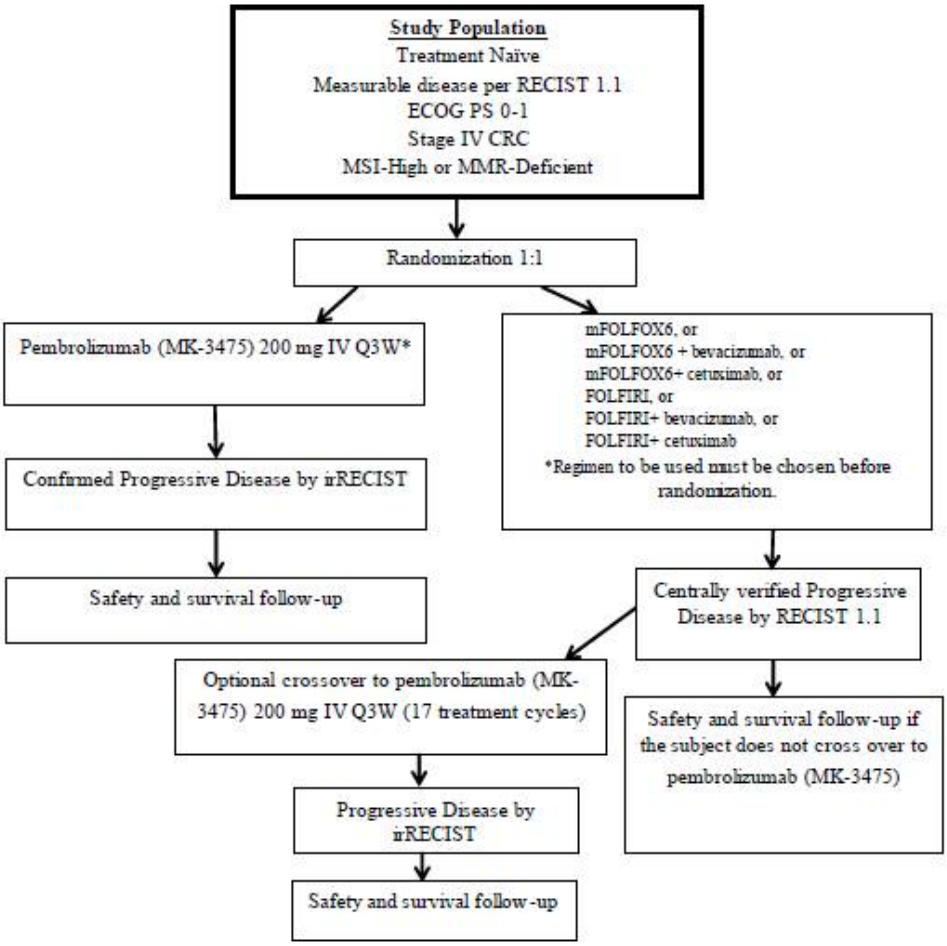
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

[redacted] An external data monitoring committee (eDMC) will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to an executive

oversight committee of the SPONSOR. The eDMC responsibilities and review schedules will be outlined in the eDMC charter.

2.2 Trial Diagram

The study design is depicted in Figure 1 below.



*For pembrolizumab (MK-3475) treatment discontinuation after CR, please refer to Section 5.8.1.

Figure 1 Study Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with stage IV MSI-H or dMMR CRC treated with first-line (1L) pembrolizumab (MK-3475) versus SOC chemotherapies,

1) **Objective**: To compare Progression-Free Survival (PFS) per RECIST 1.1 by central imaging vendor.

   Hypothesis (H1): Pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 by central imaging vendor compared to SOC chemotherapies.

2) **Objective**: To compare Overall Survival (OS).

   Hypothesis (H2): Pembrolizumab (MK-3475) prolongs OS compared to SOC chemotherapies.

The study is considered to have met its primary objective if pembrolizumab is superior to SOC chemotherapies in either of the 2 primary endpoints.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with stage IV MSI-H or dMMR CRC treated with 1L pembrolizumab (MK-3475) versus SOC chemotherapies,

1) **Objective**: To compare Overall Response Rate (ORR) per RECIST 1.1 by central imaging vendor.

   Hypothesis (H3): Pembrolizumab (MK-3475) improves ORR compared to SOC chemotherapies

2) **Objective**: To evaluate the safety and tolerability profiles.

3.3 Exploratory Objectives

1) **Objective**: To evaluate Progression-Free Survival 2 (PFS2).

2) **Objective**: To evaluate Progression-Free Survival (PFS) per irRECIST by central imaging vendor.

3) **Objective**: To evaluate Duration of Response (DOR) per RECIST 1.1 by central imaging vendor.

4) **Objective**: To evaluate score change of health-related quality-of-life using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC QLQ- CR29 from baseline among subjects treated with pembrolizumab (MK-3475) compared to SOC chemotherapies.

5) **Objective**: To characterize utilities using EuroQoL EQ-5D among subjects treated with pembrolizumab (MK-3475) compared to SOC chemotherapies.

6) **Objective**: To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumor) will be analyzed for association with clinical data collected in this study.

7) **Objective**: To evaluate the surgical conversion rate among subjects treated with pembrolizumab (MK-3475) compared to SOC chemotherapies.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1), thus, inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the current Investigator Brochure.

4.1.1 Pharmaceutical and Therapeutic Background

Microsatellite instability (MSI) is the molecular hallmark of mismatch repair deficiency, which results in high mutational load in MSI tumors and creates tumor-specific neo-antigens [1] [2], highly activated Th1- and cytotoxic T cell (CTL)-rich microenvironment with elevated expression of the gene encoding interferon gamma (IFNγ). Importantly however, offsetting this active Th1/CTL microenvironment, MSI-H tumors selectively demonstrate highly upregulated expression of multiple immune checkpoints, including programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), and indoleamine 2,3-dioxygenase (IDO), indicating the active immune microenvironment primed by neo-antigens is counterbalanced by immune inhibitory signals that hinder tumor elimination. [3], [1], [2] Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 to restore the function of the host immune response in facilitating immune mediated tumor regression and ultimately rejection – a scientifically rational therapeutic approach for MSI-H colorectal cancer. The efficacy of pembrolizumab (MK-3475) was recently studied in pretreated subjects with advanced MSI-H CRC; its impressive results are reported in the proof of concept KEYNOTE 016 (Section 4.2.2).

4.1.2 Preclinical and Clinical Studies

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 ultimately

leads 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, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFNγ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell in vivo [4] [5] [6] [7] [8] [9]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Clinical studies have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric cancer.

4.1.3 Ongoing Clinical Studies

Ongoing clinical studies of pembrolizumab (MK-3475) are being conducted in advanced melanoma, non-small cell lung cancer, and a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

4.1.4 Information on Other Study-Related Therapy

Approved drugs for colorectal carcinoma in the first-line setting include chemotherapy (fluoropyrimidines, oxaliplatin, irinotecan) and monoclonal antibodies (anti-VEGF [vascular endothelial growth factor]: bevacizumab, or anti-EGFR [epidermal growth factor receptor]: cetuximab). Table 1 lists the studies of approved drugs for colorectal cancer.

FOLFOX or FOLFIRI as first line therapy

FOLFOX and FOLFIRI have been established as SOC first-line chemotherapy options for metastatic CRC, and may be used interchangeably depending on the physician's recommendation per a subject's profile as well as institutional and regional preference. Colucci et al. established the equivalency in clinical outcomes between FOLFOX4 and FOLFIRI in a Phase III study that randomized a total of 360 chemotherapy-naive subjects to either FOLFIRI or FOLFOX4. The median time to progression (TTP; 7 vs 7 months, respectively), and median overall survival (OS; 14 vs 15 months, respectively) were similar between the 2 regimens, without statistically significant difference. [10]

The concept of either FOLFOX or FOLFIRI being used in the first-line setting, to be sequenced by the other regimens upon progressive disease is further solidified in a Phase III study performed by GERCOR. In first-line therapy, FOLFIRI achieved 8.5 months median PFS, versus 8.0 months for FOLFOX6 (p=0.26). The median survival for FOLFIRI followed by FOLFOX6 was 21.5 months in 109 subjects versus 20.6 months in 111 subjects allocated to FOLFOX6 followed by FOLFIRI (p=0.99). [11]

Bevacizumab containing therapy

Bevacizumab was studied in subjects with untreated metastatic CRC who were randomly assigned to IFL or IFL and bevacizumab. Subjects receiving the combination of IFL and bevacizumab experienced better PFS compared to IFL, 10.6 months vs 6.2 months. Overall survival was 20.3 months in the IFL plus bevacizumab group compared to 15.6 months in the IFL group. [12]

BICC-C is a multi-cohort study evaluating 3 different irinotecan-containing regimens for subjects with untreated metastatic CRC. After bevacizumab was approved, this study was amended and an additional 117 subjects were randomly assigned to receive FOLFIRI plus bevacizumab or mIFL plus bevacizumab. Although the primary endpoint, PFS, was not significantly different (FOLFIRI plus bevacizumab: 11.2 months vs. mIFL plus bevacizumab: 8.3 months; p=0.28), subjects receiving FOLFIRI and bevacizumab had a significantly better OS (not yet reached with a median follow-up of 22.6 months vs. 19.2 months, p=0.007). As such, bevacizumab can be added to FOLFIRI in the first-line setting. [13]

Even though there is no direct clinical data, bevacizumab and FOLFOX became SOC after the Intergroup study N9741 study reporting superior OS of FOLFOX versus IFL and IROX [14]. Subsequently, a Phase III study of untreated stage IV CRC was conducted; subjects were assigned in a 2x2 factorial design to CAPOX vs FOLFOX4 and then to bevacizumab vs placebo. In this study, median PFS was 9.4 months for subjects receiving either CAPOX or FOLFOX and bevacizumab, and 8 months for subjects receiving CAPOX or FOLFOX and placebo (p=0.0023). Median OS was 21.3 months for subjects receiving bevacizumab containing therapy and 19.9 months for subjects receiving placebo (p=0.077). [15]

Cetuximab containing therapies

In the CRYSTAL study, cetuximab was studied in subjects who were randomized to receive cetuximab in combination with FOLFIRI or FOLFIRI alone as first-line treatment. There was a statistically significant improvement in PFS in the combination arm compared to FOLFIRI alone (median PFS 8.9 vs 8.0 months; p=0.048). In KRAS wild-type subjects, the median PFS was 9.9 months in the combination arm compared to 8.7 months in the FOLIRI alone arm (p=0.03). [16]

In the OPUS study, subjects were randomly assigned to FOLFOX4 or FOLFOX4 plus cetuximab. There was no statistical difference in response rate or PFS. However, in the subset analysis of KRAS wild-type tumors, cetuximab was associated with a statistically significant improvement in PFS of 8.3 months vs 7.2 months (p=0.0064). [17]

More recently, in the Phase 3 FIRE3 study, subjects were randomized to FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab. Median PFS was 10 months in the cetuximab group and 10 months in the bevacizumab group (p=0.55). Median overall survival was 28.7 months in the cetuximab group compared with 25 months in the bevacizumab group (p=0.017) for KRAS exon 2 wild-type subjects. [18]

Table 1 Studies of Approved Drugs for Colorectal Cancer

Study Title	**Treatment Arms**	**N**	**Efficacy Outcomes HR, 95% CI**
Phase III Randomized Study of FOLFIRI Versus FOLFOX4 in the Treatment of Advanced Colorectal Cancer: A Multicenter Study of the Gruppo Oncologico Dell'Italia Meridionale	Arm A: FOLFOX4 Arm B: FOLFIRI	Arm A: 164 Arm B: 172	TTR Arm A: 7 months Arm B: 7 months OS Arm A: 14 months vs. Arm B:15 months
FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study	ARM A: FOLFIRI followed by FOLFOX6 Arm B: FOLFOX6 followed by FOLFIRI	Arm A: 109 Arm B: 111	OS Arm A: 21.5 months vs. Arm B: 20.6 months (p=0.99) In first-line therapy: PFS Arm A: 8.5 months vs. Arm B: 8.0 months (p=0.26)
Randomized, Controlled Study of Irinotecan Plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer: Results From the BICC-C Study	Arm A: FOLFIRI and bevacizumab Arm B: mIFL and bevacizumab	Arm A: 57 Arm B: 60	OS at median follow-up of 22.6 months Arm A: not yet reached vs. Arm B:19.2 months, (p=0.007) PFS Arm A: 11.2 months vs. Arm B: 8.3 months (p=0.28)
Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study	Arm A: CAPOX or FOLFOX and bevacizumab Arm B: CAPOX or FOLFOX and placebo	Arm A: 699 Arm B: 701	OS Arm A: 21.3 months vs Arm B: 19.9 months (p=0.077) PFS Arm A: 9.4 months vs Arm B: 8.0 months (p=0.0023)
Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer	Arm A: FOLFIRI plus cetuximab Arm B: FOLFIRI	Arm A: 599 Arm B: 599	PFS for wild-type KRAS Arm A: 9.9 months vs Arm B: 8.7 months (p=0.03) OS for wild-type KRAS Arm A: 24.9 months vs Arm B: 21 months (P not reported)

Study Title	Treatment Arms	N	Efficacy Outcomes HR, 95% CI
Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study	Wild-type KRAS Arm A: Cetuximab plus FOLFOX4 Arm B: FOLFOX4	Arm A: 82 Arm B: 97	PFS for wild-type KRAS: Arm A: 8.3 months vs Arm B: 7.2 months (p=0.0064)
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for subjects with metastatic colorectal cancer (FIRE-3): a randomized, open-label, Phase 3 study	Arm A: FOLFIRI plus cetuximab Arm B: FOLFIRI plus bevacizumab	Arm A: 297 Arm B: 295	PFS Arm A: 10.8 months vs Arm B: 10.3 months (p=0.55) OS Arm A: 28.7 months vs Arm B: 25 months (p=0.017)

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

In the United States (US), CRC is the third most common diagnosed cancer and the third leading cause of cancer death in both men and women [19]. The American Cancer Society estimated that 132,640 people will be diagnosed with CRC and 49,700 people will die from the disease in 2015. [20] Approximately 4.5% of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime. [21] Based on the Surveillance, Epidemiology, and End Results (SEER) Program data from 2008 to 2012, the age-adjusted incidence rate was 42.4 per 100,000 population; the incidence was higher in men (48.9 per 100,000 men) than in woman (37.1 per 100,000 women). [22] The incidence increased with age, from 0.1 per 100,000 in those between 10 and 14 years of age to 311.9 per 100,000 among those above 85 years of age. [21] The median age at diagnosis was 68 years. Ethnically, colorectal cancer rates are highest in black men and women and lowest in Asian and Pacific Islander (API) men and women. [21] The estimated age-adjusted prevalence proportion of colorectal cancer diagnosed in the previous 20 years on 01-JAN-2012 was 0.2845%, with an overall complete prevalence count of 1,168,929 on the same date. [22]

Similar to incidence patterns, mortality rates declined most rapidly in the past decade. The annual overall mortality for colorectal cancer was 15.5 per 100,000, and men had a higher mortality (18.6 per 100,000 men) than women (13.1 per 100,000 women) [22]. On average, the 5-year survival was 65%, and survival was highest among those with localized lesions (90.1%), followed by those with regional lesions (70.8%), and was the lowest among those with distant lesions (13.1%). [21]

Colorectal cancers may be divided via molecular phenotyping into tumors with normal DNA mismatch repair (MMR) function and those with DNA MMR deficiency (MMR-D) [23]. Tumors showing the presence of MSI are classified as MSI-H (high) depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as microsatellite-stable (MSS). [24] The prevalence estimates of MSI-H in all CRC subjects were similar across studies, ranging between 14% and 16%. In one population-based study,

which included 2,080 persons diagnosed with incident invasive CRC between January 1998 and June 2002, residing in one of the 3 counties of Washington State, US, approximately 16% of all the cases had tumors that were MSI-H. [25]

Germline mutations in MMR genes cause a cancer susceptibility syndrome called Lynch syndrome. Germline mutations in the MMR genes MLH1, MSH2, MSH6 and/or PMS2 or EpCAM are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases. [26] Many studies have found that some CRCs occurring in non-Lynch syndrome subjects also showed MSI (sporadic CRCs with MSI), and CRCs with MSI showed different clinical-pathological features, prognosis, and response to chemotherapeutic agents compared to microsatellite-stable CRCs. [27]

MSI-H CRC comprises approximately 15% of sporadic CRC and 5% of stage IV CRC, whereas MSS CRC comprises the remainder. [28] [29] The estimates for MSI-H CRC in stage IV subjects range from ~3.5% to 5%. Zsofia et al, indicated when assessed stage –by-stage, the presence of MSI-H is noted in ~20% of stage I/II, ~12% of stage III, but only ~4% of stage IV subjects. [23] Data from the PETACC-3 study showed that tumor specimens characterized as MSI-H are more common in stage II disease than in stage III (22% vs. 12% respectively; p<0.0001).[30] The study by Koopman et al, indicated that the percentage of stage IV tumors characterized as MSI-H was only 3.5%. [31]

A recent study reported that once the disease recurs the prognostic advantage of MSI-H CRC is lost as the median OS after recurrence in stage II disease is 1.6 versus 2.2 years (MSI-H CRC vs MSS CRC, respectively; hazard ratio (HR) 1.00, 95% confidence interval (CI), 0.68-1.48; p>0.99) and after stage III disease is 1.2 versus 1.6 years (MSI-H CRC versus MSS CRC, respectively; HR 1.00, 95% CI, 0.85-1.17; p>0.99). The same group reported that there is actually a disadvantage in having MSI-H status in advanced disease. Five percent of the primary tumors of 3,063 subjects, pooled from 4 Phase III first-line studies in CRC, were found to be MSI-H. The median PFS and OS were significantly worse for subjects with MSI-H CRC compared with proficient MSS tumors (PFS: 6.2 vs 7.6 months; HR 1.33, 95% CI, 1.12-1.57; p=0.001; OS: 13.6 vs 16.8; HR 1.35, 95% CI, 1.13-1.61; p=0.001). [32] These data emphasize that the prognosis for subjects with metastatic MSI-H CRC is poor despite the current treatment options. Therefore, advanced or metastatic MSI-H CRC subjects represent a group of subjects with a high unmet medical need.

4.2.2 Proof of Concept: Keynote 016 (KN016)

4.2.2.1 Overview of Efficacy in KN016 study

KN016 evaluated pembrolizumab (MK-3475) monotherapy in MSI-H CRC and MSS as well as MSI-H non-CRC subjects [33]. A total of 48 subjects were enrolled and treated during the period from September 2013 through May 2015. As of May 2015, the study accrued 13 MSI-H, 25 MSS CRC, and 10 MSI-H non-CRC subjects. All CRC subjects had received >2 prior chemotherapy regimens (median=4) except for one MSS subject who had received 1 chemotherapeutic and 1 immunotherapeutic (non-PD-1-based) regimen. The subjects received pembrolizumab (MK-3475) 10mg/kg every 2 weeks. Radiologic assessments were made using RECIST v1.1 and immune-related response criteria (irRC) at 12 weeks and then every 8 weeks thereafter.

Mismatch repair status was assessed in tumors through the evaluation of selected microsatellite sequences that are particularly prone to copying errors when mismatch repair is compromised or by immunohistochemistry to determine expression of MMR proteins. Thus MSI tumor status was classified as MSI-H when ≥2 loci were present among the 5 analyzed microsatellite loci (NR-21, BAT-26, BAT-25, NR-24, and MONO-27) as detected by polymerase chain reaction (PCR) (Promega MSI analysis system) or if 1 or more of the 4 (MLH1/MSH2/MSH6/PMS2) mismatch repair protein expression [as detected by immunohistochemistry (IHC)] was absent.

In the 13 subjects with MSI-H CRC, the ORR was 62%, whereas in 25 subjects with MSS CRC, no objective response was observed (ORR 0%). In the 10 MSI-H non-CRC subjects, the ORR was also 60%, demonstrating that pembrolizumab (MK-3475) is effective in all MSI-H subjects irrespective of the tumor type (Table 2).

As shown in Figure 2, decreased serum tumor markers were observed in MSI-H CRC and non-CRC subjects, but not in MSS CRC subjects and reduction corresponded with clinical benefit. Radiographic responses are shown in Figure 3. The majority of MSI-H CRC (green bars) and MSI-H non-CRC subjects (black bars) experienced tumor shrinkage whereas MSS subjects (red bars) experienced no tumor shrinkage.

Data presented in Figure 4 and Figure 5 show that the DOR observed in both MSI-H CRC and MSI-H non-CRC subjects is remarkably long in this advanced disease setting compared with MSS CRC subjects. In addition, none of the 8 out of 13 MSI-H CRC subjects with PR have progressed at the time of this report (longest DOR is 16+ months).

Kaplan Meier curves for PFS and OS are shown in Figure 6 Panels A and B and Figure 7 Panels C and D respectively. For the subjects with MSI-H CRC, median PFS and median OS were not reached. In contrast, the subjects with MSS CRC had a median of PFS 2.3 months and a median of OS 7.6 months. The HR for PFS (MSI-H vs. MSS) is 0.13 ($p<0.0001$, 95% CI [0.07, 0.36]). The HR for OS (MSI-H vs. MSS) is 0.17 ($p<0.007$, 95% CI [0.09, 0.68]).

Table 2 Objective Responses for Subjects Enrolled in KN 016

	MSI-H CRC	MSS CRC	MSI-H non-CRC
Type of Response-no. (%)	13	25	10
Complete Response[1]	0 (0)	0 (0)	1 (10)
Partial Response[2]	8 (62)	0 (0)	5 (50)
Stable Disease (Week 12)	4 (30)	4 (16)	1 (10)
Progressive Disease	1 (8)	14 (56)	2 (20)
Not Evaluable[3]	0 (0)	7 (28)	1 (10)
Objective response rate	62%	0%	60%
95% CI	32-86	0-14	26-88
Disease control rate[4]	92%	16%	70%
95% CI	64-100	5-36	35-93

[1]One endomestudy subject in the MSI-H non-CRC cohort who was originally a PR achieved CR subsequently.
[2]Eight CRC subjects in the MSI-H CRC cohort and 5 subjects in the MSI-H non-CRC (endomestudy, ampullary, duodenum, cholangio, and gastric cancers) achieved PR.
[3]Subjects were considered not evaluable if they did not undergo a 12-week scan due to clinical progression. Seven subjects in the MSS CRC cohort and 1 subject in the MSI-H non-CRC cohort were found to be not evaluable.
[4]The rate of disease control was defined as the percentage of subjects who had a complete response, partial response, or stable disease for 12 weeks or more.

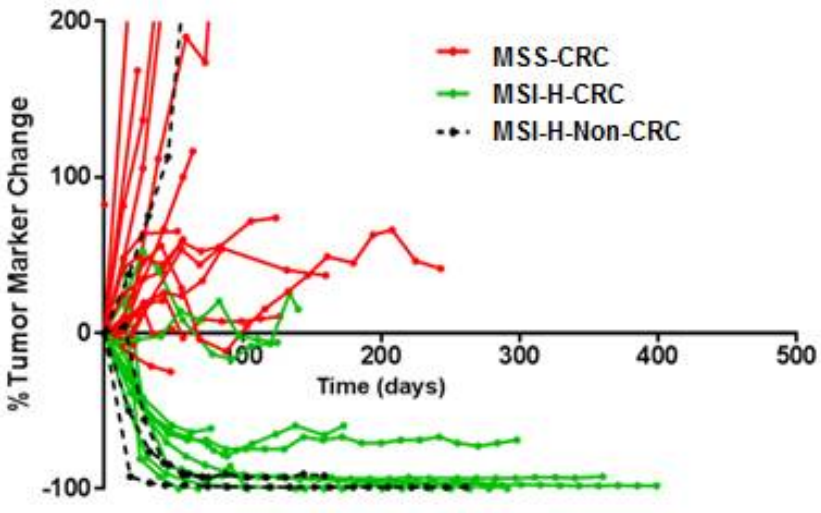


Figure 2 Biochemical Responses

Serum protein biomarker levels were measured with each cycle and the values represent percent change from baseline. Subjects were included if baseline tumor marker values were greater than the upper limit of normal. CA-125 was used for a subject with endometrial cancer; CA19-9 was used for one cholangiocarcinoma and one ampullary cancer; and carcinoembryonic antigen (CEA) was used for all other subjects. Red, green, and black lines represent subjects with MSS, MSI-H CRC, and MSI-H non-CRC, respectively.

Figure 3 Radiographic Responses

Tumor responses were measured at regular intervals and values show the best fractional change of the sum of longest diameters (SLD) from the baseline measurements of each measurable tumor.

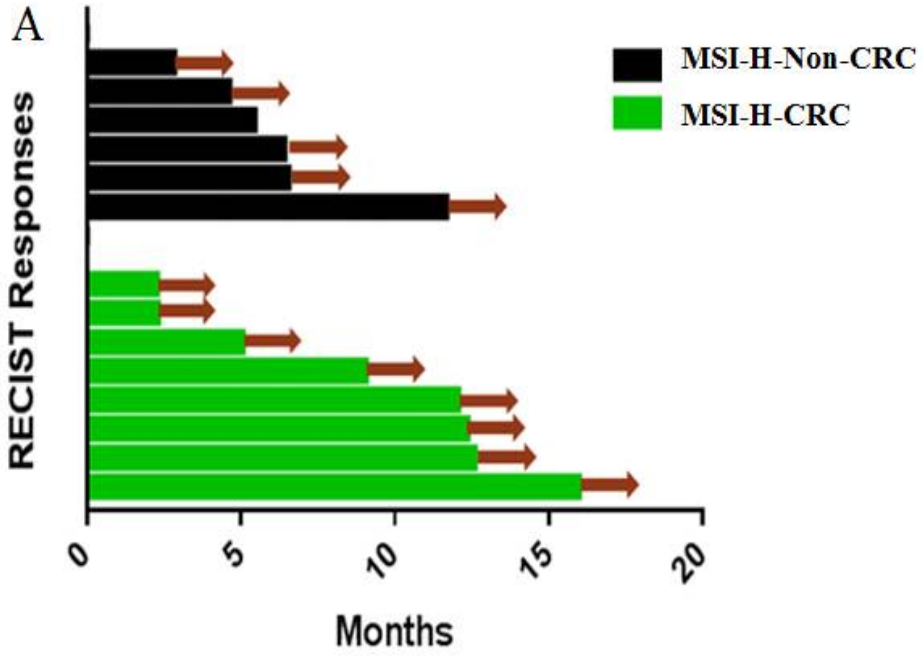


Figure 4 Duration of Objective Response

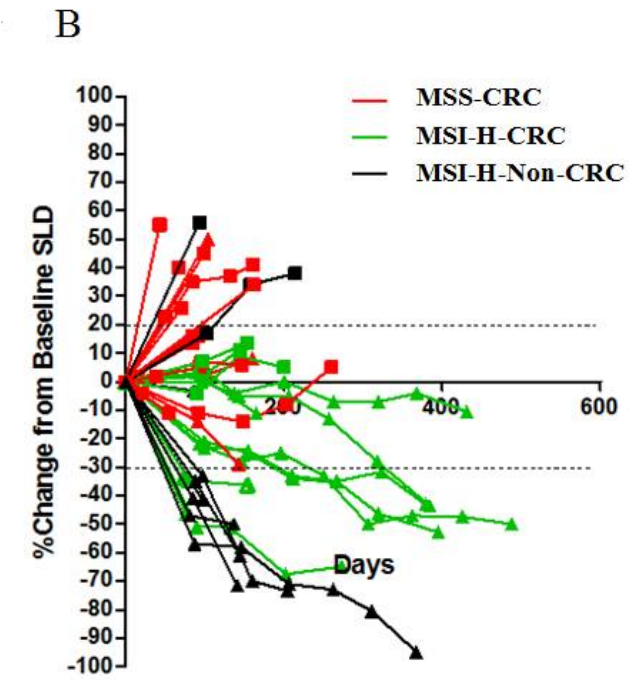


Figure 5 Duration of Disease Control

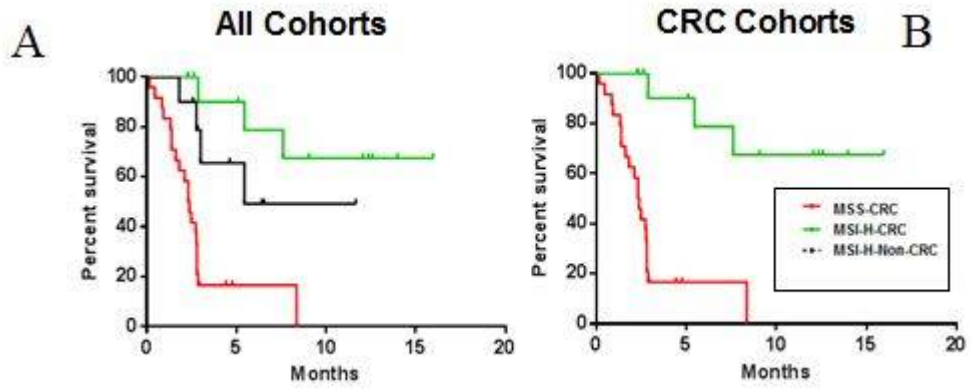


Figure 6 A and B Progression-Free Survival

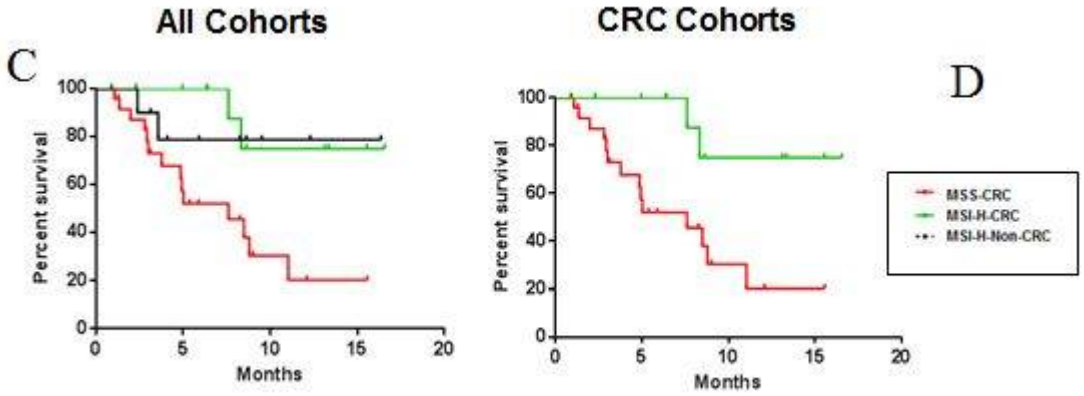


Figure 7 C and D Overall Survival

In summary, dMMR/MSI-H tumors were highly responsive to pembrolizumab (MK-3475). Biochemical response correlates with radiographic response as well as with PFS and OS. The overall results from the KN016 study suggest that MSI status predicts clinical benefit of immune checkpoint blockade with pembrolizumab (MK-3475) in both CRC and non-CRC subjects.

4.2.2.2 Overview of Safety in KN016 study

Adverse events occurring in more than 5% of the subjects are listed in Table 3 below. Events of clinical interest included rash or pruritus (17%); thyroiditis, hypothyroidism (10%), hypophysitis (2%); and asymptomatic pancreatitis (15%). Although the numbers were small, thyroid-function abnormalities were limited to the cohorts with mismatch repair–deficient cancer. There were no treatment-related serious adverse events. The overall adverse event summary as of 28-JAN-2015 appears in Table 3.

Table 3 Adverse Event Summary: KN016

Adverse Event	All Grades no. (%) N=41	Grades 3 or 4 no. (%) N=41
Any	21 (51)	4 (10)
Generalized symptoms		
Fatigue	1 (2)	0 (0)
Myalgias	1 (2)	0 (0)
Arthalgias	1 (2)	0 (0)
Pancreatitis[1]	6 (15)	0 (0)
Pneumonitis	1 (2)	0 (0)
Endocrine disorders		
Thyroiditis/hypothyroidism	4 (10)	0 (0)
Hypophysitis	1 (2)	0 (0)
Rash/pruritis	7 (17)	0 (0)
Thrombocytopenia	1 (2)	1 (2)
[1] All cases of pancreatitis were asymptomatic.		

4.2.3 Rationale for Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- clinical data from 8 randomized studies demonstrating flat dose and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- clinical data showing meaningful improvement in benefit-risk including OS at Q3W across multiple indications, and
- pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small-cell lung cancer (NSCLC), covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2, and KN006). All of these studies demonstrated flat dose and exposure-response relationships across the doses studied representing an approximate 5 to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose/exposure-response relationships were also observed in other tumor types, including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacologic data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dose regimen provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed-dose regimen and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose regimen has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose regimen was selected for evaluation across all pembrolizumab protocols.

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

4.2.3.1 Rationale for the Use of Comparator

Comparators in this study include mFOLFOX6 or FOLFIRI or respective combinations with bevacizumab or cetuximab; all are globally accepted standards of care as recommended by formal guidelines [National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and Japanese Society for Cancer of the Colon and Rectum (JSCCR)].

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

This study will use PFS and OS as the primary endpoints. PFS is an acceptable measure of clinical benefit for a randomized Phase III study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. The endpoint of OS is the standard for demonstrating superiority of antineoplastic therapy in oncology clinical studies.

RECIST 1.1, as assessed by the central imaging vendor, will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Since the treatment assignment is unblinded, images read by the central imaging vendor blinded to treatment assignment can minimize bias in the response assessments. In addition, final determination of radiologic PD will be based on the central imaging vendor assessment of PD, rather than local site Investigator/radiology assessment. Verification of PD will be expedited by the central imaging vendor and communicated to the site study team and Sponsor.

4.2.4.2 Exploratory Endpoints

4.2.4.2.1 Immune-Related RECIST (irRECIST)

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Based on an analysis of subjects with melanoma enrolled in KEYNOTE-001, 7% of evaluable subjects experienced delayed or early tumor pseudoprogression. Of note, subjects who had progressive disease by RECIST 1.1, but not by immune-related response criteria, had longer OS than subjects with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab (MK-3475) in approximately 15% of subjects. 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 enable treatment beyond initial radiographic progression. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response

seen with immuno-therapeutics as described in [34]. 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 local site Investigators to assess tumor response and progression, and make treatment decisions as well as by the central imaging vendor in support of the PFS endpoint. (See section 7.1.4.6 for additional details on irRECIST assessments).

4.2.4.2.2 Subject Reported Outcomes (PRO)

As part of an exploratory analysis, subjects will provide information regarding their health-related quality-of-life (HRQoL) via the following EORTC assessment tools: EORTC QLQ-C30 and QLQ-CR29, and eEuroQol-5D3L (EQ5D-3L) questionnaires. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

eEORTC QLQ-C30 and eEORTC QLQ-CR29

The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functioning dimensions (physical, role, cognitive, emotional, and social), 3 symptom items (fatigue, nausea/vomiting, pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality-of-life scale. [35] This instrument has been translated and validated into 81 languages and used in more than 3,000 studies worldwide.

The EORTC QLQ-CR29, a supplemental colorectal cancer-specific module, comprises multi-item and single-item measures of colorectal cancer-associated symptoms and impact. It includes 4 scales assessing urinary frequency, fecal seepage, stool consistency, and body image, and single items assessing other common problems following treatment of colorectal cancer.

eEuroQoL-5D

The eEuroQol-5D-3L (eEQ5D-3L) is a standardized instrument for use as a measure of health outcome. The eEQ5D-3L will provide data for use in economic models and analyses including developing health utilities or quality adjusted life years (QALYs). The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-point scale from 1 (extreme problem) to 3 (no problem). The eEQ5D-3L 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 eEQ5D-3L will always be completed by subjects first before completing the EORTC QLQ-C30 and QLQ-CR29 and is to be completed at various time points as specified in the Study Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

See flow chart for PRO assessment schedule.

4.2.4.3 Safety Endpoints

The safety objective of this study is to characterize the safety and tolerability of pembrolizumab (MK-3475) in subjects with MSI-High or dMMR CRC. 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 (MK-3475) compared to SOC including SAEs.

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.

4.2.4.4 Microsatellite Instability Testing

Microsatellite instability (MSI), a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers. MMR proteins, or MSI loci testing for CRC is clinically indicated as per NCCN, ESMO, and American Society of Clinical Oncology (ASCO) guidelines. [26] [36] [37] MMR or MSI status is determined by examining either 1) protein expression by IHC of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 2) 3-5 tumor microsatellite loci using PCR-based assay, respectively.

Tumors are classified as MSI high when at least 2 allelic shifts among the 3-5 analyzed microsatellite markers are detected by PCR, or absence of at least 1 of 4 MMR enzymes' protein expression is detected by IHC.

4.2.4.5 Planned Exploratory Biomarker Research

Planned Genetic Analysis

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

Additional biomarker research to identify factors important for pembrolizumab (MK-3475) therapy may also be pursued. For example, tumor and blood samples from this study may undergo proteomic, genomic, metabolomics, and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab (MK-3475) therapy and other immunologic targets.

Assays may include but are not be limited to:

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material will be completed to assess expression of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab (MK-3475). The hypothesis to be tested is that pembrolizumab (MK-3475) induces responses in tumors that reflect an inflamed/immune phenotype based on gene expression signatures capturing interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (eg, IL-10). MicroRNA profiling may also be pursued in serum samples.

Proteomic analysis

Tissue derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in subject selection for pembrolizumab (MK-3475) therapy.

Gene Analyses

The application of new technologies, such as next-generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being hypermutated (also known as increase mutational burden) or it can detect the presence of specific t-cell clones within the tumor microenvironment. Increased mutational burden is one of the major mechanisms of neo-antigen presentation in the context of a tumor. The increased presence of foreign-like peptides due to somatic mutations in the DNA of the tumor increases the chances that the tumor will be visible to the adaptive immune system through the major histocompatibility complex I (MHC-I) antigen presentation mechanism. There are a number of mechanisms by which a tumor can have increased mutational burden such as defects in key genes related to DNA mismatch repair mechanisms or environmentally induced factors such as smoking. Additionally, a DNA tetrapeptide neo-antigen mutational signature pattern can also be obtained by use of bioinformatics prediction tools of HLA-restricted mutated peptide binding to MHC class I and to the T-cell. There is a potential that an increased hypermutated state, the presence of neo-antigen mutational patterns and the detection of increased T-cell clonality, all of which can be determined by use of next-generation sequencing methods, may correlate with response to pembrolizumab (MK-3475) therapy and/or that the converse, hypomutated state (the absence of neo-antigens) may correlate with non-response.

4.2.4.6 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

Subjects in clinical studies generally cannot expect to receive direct benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. France only: It cannot be guaranteed that subjects in clinical studies will directly benefit from treatment during participation, as clinical studies 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 study may be found in the accompanying IB and informed consent documents.

Based on results from the ongoing clinical studies, there is no contraindication to the continued clinical investigation of pembrolizumab.

In addition, beneficial effects of pembrolizumab have been seen in several studies to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma both in a single-arm study encompassing nearly 1000 subjects (KEYNOTE 001), which led to USFDA approval in September 2014, and in a randomized comparison to chemotherapy (KEYNOTE-002 – detailed in the IB). Additional potential benefits for CRC were demonstrated in the proof-of-concept study KEYNOTE-016, which showed that dMMR/MSI-H CRC were highly responsive to pembrolizumab (MK-3475) monotherapy (refer to Section 4.2.2.1).

In conclusion, pembrolizumab demonstrates a promising anticancer activity in MSI-H/dMMR CRC subjects with an acceptable safety profile compared to those of existing therapeutic options. Ongoing and planned studies will allow for a more comprehensive analysis of benefit/risk balance of pembrolizumab.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer will be enrolled in this study.

5.1.2 Subject Inclusion Criteria

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

1. Provide written informed consent for the study.

2. Be male or female who is ≥ 18 years of age on the date of signing informed consent.

3. Have locally confirmed MMR deficient (dMMR) or microsatellite instability-high (MSI-H) stage IV colorectal carcinoma (refer to Section 4.2.4.4 for details).

4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 10 days prior to treatment initiation.

5. Have life expectancy of at least 3 months.

6. Have measurable disease at baseline based on RECIST 1.1 as determined by the local site Investigator/radiology assessment.

7. Female subjects of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication.

8. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study starting with the first dose of study medication through 180 days after the last dose of study medication for the chemotherapy arm and 120 days for pembrolizumab (MK-3475) arm, whichever is later.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of study medication through 180 days after the last dose of study medication for the chemotherapy arm and 120 days for pembrolizumab (MK-3475) arm, whichever is later.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

10. Demonstrate adequate organ function as defined in Table 4. All screening laboratory assessment should be performed within 10 days prior to treatment initiation.

Table 4 Adequate Organ Function Lab Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance [Glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl)]	≤1.5 × upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 ULN
Aspartate aminotransferase (AST) [Serum glutamic oxaloacetic transaminase (SGOT)] and Alanine Aminotransferase (ALT) [Serum Glutamic Pyruvic Transaminase (SGPT)]	≤2.5 × ULN **OR** ≤5 × ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or partial prothrombin time (PTT) is within therapeutic range of intended use of anticoagulants
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
[a] 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. Has received prior systemic therapy for stage IV CRC. Subjects may have received prior adjuvant chemotherapy for CRC as long as it was completed at least 6 months prior to randomization.

2. Is currently participating and receiving study medication in another study, or has participated in a study of an investigational agent and received study medication, or used an investigational device within 4 weeks of randomization.

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

4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.

5. Has had radiation therapy within 4 weeks prior to randomization of study medication and who has not recovered to baseline from adverse events due to radiation therapy. Subjects who have been given palliative radiotherapy to peripheral sites (eg, bone metastasis) may enter the study before 4 weeks have elapsed but must have recovered from any acute adverse effects.

6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable brain metastases (without evidence of progression by imaging as confirmed by magnetic resonance imaging [MRI] if MRI was used at prior imaging, or confirmed by computed tomography [CT] imaging, if CT used at prior imaging, at least 4 weeks prior to the first dose of study medication; also, any neurologic symptoms must have returned to baseline], and have not used steroids for brain metastases for at least 28 days prior to study initiation. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7. Has had major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization.

8. Has received prior therapy with an immune checkpoint inhibitor (eg, anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or anti-CTLA-4 agent, etc).

9. Has another malignancy that is progressing or requires active treatment. Exceptions include non-melanomatous skin cancer that has undergone potentially curative therapy and in situ cervical carcinoma.

10. Has received a live vaccine within 30 days of planned start of study medication (see Section 5.5.2).

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

    - France and UK only: Has a history or current evidence of any condition, (ie, known allergy, hypersensitivity, or contraindication to fluorouracil, leucovorin, oxaliplatin, irinotecan, bevacizumab, or cetuximab or any components used in their preparation if

such is applicable in the investigator's choice of chemotherapy for this study), therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

12. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active chronic or acute Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

13. Has known history of, or any evidence of interstitial lung disease or active, non-infectious pneumonitis.

14. Has a known history of active tuberculosis (TB; *Bacillus tuberculosis*).

15. Has an active infection requiring systemic therapy.

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

17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study medication for SOC or 120 days after the last dose of study medication in the pembrolizumab (MK-3475) arm.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 5.

Table 5 Study Medication

Study Medication	Dose/Potency	Dose Frequency	Route of Administration	Use
Pembrolizumab (MK-3475)	200 mg IV over 30 minutes	Q3W	IV infusion	Experimental
mFOLFOX6	mFOLFOX6: Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/ m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion	Q2W	IV infusion	Standard of care
mFOLFOX6 + bevacizumab	mFOLFOX6: Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion Bevacizumab 5 mg/kg IV, day 1	Q2W	IV infusion	Standard of care
mFOLFOX6 + cetuximab	mFOLFOX6: Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 Leucovorin* 400 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/m^2 IV bolus, day 1, then 5-FU 1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours) IV continuous infusion Cetuximab: 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 1 hour weekly	Q2W	IV infusion	Standard of care

Study Medication	Dose/Potency	Dose Frequency	Route of Administration	Use
FOLFIRI	FOLFIRI: Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion	Q2W	IV infusion	Standard of care
FOLFIRI +bevacizumab	FOLFIRI: Irinotecan 180 mg/m^2 IV over 30-90 mins, day 1 Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/ m^2 over 46-48 hours) IV continuous infusion Bevacizumab 5 mg/kg IV, day 1	Q2W	IV infusion	Standard of care
FOLFIRI +cetuximab	FOLFIRI: Irinotecan 180 mg/m^2 IV over 30-90 mins, day 1 Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion Cetuximab: 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 1 hour weekly	Q2W	IV infusion	Standard of care
*or levoleucovorin 200mg/m^2				

Trial Treatment should begin within 3 days of randomization. However every effort should be made to begin study medication on the day of randomization.

All supplies indicated in Table 5 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number.

Per local guidelines the trial site may be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of the dose of pembrolizumab (MK-3475) to be used in this study is provided in Section 4.0, Background and Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

Preparation and administration of SOC should follow local treatment guidelines.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

SOC Arm

All SOC regimens must start at doses stipulated in the protocol. Dose modifications are permitted only if the modification is due to an AE/toxicity and must follow local treatment guidelines. Oxaliplatin may be stopped and restarted to prevent neuropathy per OPTIMOX study after a minimum of 6 cycles of mFOLFOX [38]. Oxaliplatin should be resumed after 12 cycles of 5FU/leucovorin if no neuropathy occurs.

5.2.1.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Pembrolizumab (MK-3475) Arm

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These 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 study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring 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
	Recurrent Grade 2 or Grade 3 or 4	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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring 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	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• 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 [a]		
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 [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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. Table 7 provides treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 7 Infusion Reaction 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 infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study medication administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine** 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 medication administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Other allowed dose interruption for pembrolizumab

Dosing interruptions are permitted with Sponsor consultation in the case of medical/surgical events or logistical reasons not related to study medication (eg, elective surgery (including surgery for curative intent), unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study medication within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. As such, a maximum of 6 weeks between doses of pembrolizumab and a maximum of 5 weeks between doses of SOC are allowed. A scheduled dosing interruption of longer than the aforementioned requires written Sponsor approval.

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 (MK-3475) Administration

Pembrolizumab (MK-3475) 200 mg will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab (MK-3475) preparation of the infusion fluid and administration.

Every effort should be made to begin the first dose of study medication on the day of randomization, but if this is not achieved, study medication should be initiated no later than 3 days from the date of randomization.

All subsequent cycles of study medication may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the Investigator's judgment.

All study medications will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as detailed on the Study Flow Chart – Section 6.0.

All study medications will be administered on an outpatient basis.

5.2.2.2 Standard of Care

mFOLFOX6 is a regimen containing oxaliplatin, leucovorin, and 5-FU. Oxaliplatin 85 mg/m^2 is administered over 2 hours on Day 1. Leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2) IV is administered over 2 hours on Day 1. 5-FU 400 mg/m^2 is administered as an IV bolus on Day 1, then 1200 mg/m^2/day for 2 days (total 2400 mg/m^2 over 46-48 hours) IV continuous infusion. mFOLFOX6 is repeated every 2 weeks.

FOLFIRI is a regimen containing irinotecan, leucovorin, and 5-FU. Irinotecan 180 mg/m^2 is administered over 30 to 90 minutes on Day 1. Leucovorin 400 mg/m^2 (or levoleucovorin 200mg/m^2) IV infusion is administered to match duration of irinotecan infusion on Day 1. 5-FU 400 mg/m^2 is administered as an IV bolus Day 1, then 1200 mg/m^2/day for 2 days (total 2400 mg/ m^2 over 46-48 hours) IV continuous infusion. FOLFIRI is repeated every 2 weeks.

Bevacizumab 5mg/kg IV infusion is administered on Day 1 of every 2-week cycle. The first infusion is administered over 90 minutes. The second infusion is administered over 60 minutes if the first infusion is tolerated. All subsequent infusions are administered over 30 minutes if the infusion over 60 minutes is tolerated. Variations in infusion schedule per tolerability may be followed per institutional practice.

Cetuximab 400 mg/m^2 IV infusion is administered over 120 minutes for the first infusion on Day 1, then 250 mg/m^2 IV infusion over 60 minutes weekly thereafter.

All study medications will be administered on an outpatient basis.

5.2.3 Trial Blinding/Masking

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

Imaging data will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment.

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab (MK-3475) or SOC, respectively.

5.4 Stratification

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

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 is required.

5.5.1 Acceptable Concomitant Medications and Therapy

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 local and institutional standards of medical care. In addition, local therapy for palliation is permitted after consultation with the Sponsor. 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 study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications taken by the subject from the date of first dose of study medication and 30 days after the last dose of study medication should be recorded. Concomitant medications administered more than 30 days after the last dose of study medication should be recorded for SAEs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications and Therapy

Subjects are prohibited from receiving the therapies listed below during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this study.

- Antineoplastic systemic chemotherapy or immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab (MK-3475)
- Local therapy for palliation after consultation with Sponsor
- Live vaccines within 30 days prior to the first dose of study medication and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are

generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

- For pembrolizumab (MK-3475): glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids (prednisone 10 mg orally per day, or equivalent) may be approved after consultation with the Sponsor.
    - Note: Inhaled steroids are allowed for the management of asthma
    - Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, to IV contrast dye) is permitted.

Subjects may receive other medications that the Investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this study.

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

5.5.2.1 Prohibited Concomitant Medications and Therapies for UK Only

- For subjects receiving 5-FU:
    - 5-FU may not be taken or used in conjunction with:
        - Brivudine, Sorivudine analogs, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD)
        - Active immunizations
        - Polio vaccines
- For subjects receiving Leucovorin:
    - Calcium folinate may not be mixed with 5-fluorouracil in the same intravenous injection or infusion since a precipitate can be formed
    - Calcium folinate solutions should not be mixed with infusions containing hydrogen carbonate due to chemical incompatibilities
    - Incompatibilities between the injected forms of calcium folinate and the injectable forms of Droperidol, 5-fluorouracil, Foscarnet, and Methotrexate were reported
- For subjects receiving Oxaliplatin:
    - None

- For subjects receiving Irinotecan:
    - Concomitant administration of inhibitors (eg, Ketoconazole) or inducers (eg, Carbamazepine, Phenobarbital, Phenytoin, or Rifampicin) of cytochrome P-450 isoenzyme 3A activity may alter the metabolism of Irinotecan and should be avoided
    - Hypericum perforatum (Hypericum, St John's wort) preparations lower SN-38 plasma levels. Consequently Hypericum preparations should not be administered with Irinotecan
- For subjects receiving Bevacizumab:
    - None
- For subjects receiving Cetuximab:
    - None

5.6 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator.

5.6.1 Supportive Care Guidelines for Pembrolizumab (MK-3475)

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 5.2.1.2, Table 6. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab (MK-3475).

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

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.

5.7.2 Contraception

Pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (MK-3475) has transient adverse effects on the composition of sperm.

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

Female subjects will be considered of non-reproductive potential if they meet 1 of the following criteria:

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

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

- Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving pembrolizumab (MK-3475) and for 120 days after the last dose of study drug. For the chemotherapy arm, subjects should start using birth control from the first dose of chemotherapy throughout the study period up to 180 days after the last dose of study drug For subjects who cross over from chemotherapy to pembrolizumab (MK-3475), the aforementioned will apply to either 180 days after the last dose of chemotherapy or 120 days after the last dose of pembrolizumab (MK-3475), whichever is later. Subjects must comply with one of the following:

- Practice abstinence from heterosexual activity;

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

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

Acceptable methods of contraception are‡:

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

For countries (eg, Sweden and Norway) or sites that follow the Clinical Study Facilitation Group (CTFG) guidance, please use the following:

Pembrolizumab, bevacizumab, FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI (irinotecan + 5-FU + leucovorin), and cetuximab may have adverse effects on a fetus in utero. Furthermore, it is not known if these therapies have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the CTFG Guidance (Final Version 2014-09-15,

Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Subjects should start using birth control from study Visit 1 throughout the study period up to 180 days after the last dose of study medication.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2 (Reporting of Pregnancy and Lactation to the Sponsor). If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly pregnancy testing is recommended per local standards if applicable.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment, the subject will immediately discontinue treatment and be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner at any time during treatment, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.2 (Reporting of Pregnancy and Lactation to the Sponsor).

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab (MK-3475) is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

Standard of care subjects should follow label guidance for use during nursing.

5.7.5 UK Only: Sun Exposure Caution

Prolonged exposure to sunlight is not advisable in subjects treated with 5-FU due to the risk of photosensitivity.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.5 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up

- (France only): Any progression or recurrence of another malignancy, or any occurrence of another malignancy that requires active treatment.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Confirmed radiographic PD as outlined in Section 7.1.4.5 for SOC arm and Section 7.1.4.6 for pembrolizumab (MK-3475) arm (exception if Sponsor approves treatment continuation for subjects on pembrolizumab) (France only: exception does not apply).
- Unacceptable adverse experiences as described in Section 7.2.
- Intercurrent illness that prevents further administration of treatment (France only: other than another malignancy as noted above).
- Investigator's decision to discontinue the subject from treatment
- The subject has a confirmed positive serum pregnancy test (Refer to Section 5.7.3)
- Administrative reasons
- Completed 35 treatments (approx. 2 years) with pembrolizumab (MK-3475) (Initial Treatment/Crossover Phase)

The End of Treatment and Follow-up visit procedures are listed in Section 7.1.6.5 and the Study Flow Chart and Section 6.0. After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described in Section 7.2. See Section 7.2 for complete details of reporting requirements of adverse events and pregnancy/lactation.

All subjects (including subjects who have received the maximum 35 pembrolizumab treatments) will have post-treatment follow-up for disease status, until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to 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 9 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Pembrolizumab (MK-3475) after Complete Response

During the Initial Treatment Phase, discontinuation of pembrolizumab (MK-3475) may be considered for subjects who have attained a locally confirmed CR that have received at least 8 pembrolizumab (MK-3475) treatments (approximately 6 months), and had at least 2 treatments beyond the date when the initial CR was declared. Subjects who stop treatment

and then experience radiographic PD may be eligible for up to 17 additional treatments (approximately 1 year) with pembrolizumab (MK-3475) in the Second Treatment Course Phase at the discretion of the Investigator if:

- No cancer treatment was administered since the last dose of pembrolizumab (MK-3475)
- The subject meets the parameters listed in the Inclusion/Exclusion criteria
- The study is ongoing

Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.6.3. Response or progression in this Second Course Phase will not count towards the primary endpoint in this study.

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).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

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. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug.

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

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase: Pembrolizumab (MK-3475) Arm

Details regarding the procedures listed in this table are outlined in Section 7.0.

Study Period:	Screening Phase		Treatment Cycles **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures														
Informed Consent	X													
Informed Consent for Future Biomedical Research (optional)		X												
Inclusion/Exclusion Criteria		X												
Subject Identification Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X		
Survival Status[c]			←										→	X
Clinical Procedures/Assessments														
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	
ePROs (HRQoL Measures: EQ5D-3L, EORTC QLQ-C30, EORTC QLQ-CR29)[d]			X	X	X	X	X		X		X	X		
Full Physical Examination		X									X			
Directed Physical Examination			X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs		X[e]	X	X	X	X	X	X	X	X	X			

Study Period:	Screening Phase		Treatment Cycles **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
12-Lead Electrocardiogram		X												
ECOG Performance Status		X[f]	X	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status													X	X
Pembrolizumab (MK-3475) Administration			X[b]	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments														
MSI/MMR Status[g]	X													
Pregnancy Test – Serum β-HCG		X[h]	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT		X[f]												
CBC with Differential[i,j]		X[f]	X	X	X	X	X	X		X	X	X		
Chemistry Panel[i,j]		X[f]	X	X	X	X	X	X		X	X	X		
Urinalysis[i,k]		X[f]		X		X		X		X	X	X		
T3 or FT3, FT4, TSH[i,k]		X[f]		X		X		X		X	X	X		
Serum Tumor Marker (CEA)[l]			X	X							X	X		
CENTRAL Laboratory Assessments														
Blood for Genetics (DNA)[m,n]			X											
Blood for Correlative Studies (DNA and RNA)[n]			X	X	X						X			
Blood for Biomarker Studies (plasma and serum)[o]			X											
Tumor Tissue Collection														
Tumor Tissue[p]		X												

Study Period:	Screening Phase		Treatment Cycles **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Efficacy Measurements														
Tumor Imaging		X	X[q]								X[r]		X[r]	

a. After the start of new anticancer therapy, contacts are made by telephone Q9W.
b. Cycle 1 treatment must be given within 3 days of randomization (however, every effort should be made to start the first dose on day of randomization). The window for each visit is ± 3 days unless otherwise noted. For Imaging ONLY: the visit window is ± 7 days and should follow calendar days and not be adjusted for cycle delays.
c. After documented disease progression, or the start of new anticancer treatment; contacts are approximately every 9 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 subjects 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 subjects who have a death event previously recorded).
d. It is strongly recommended that electronic subject reported outcomes (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ5D-3L, followed by EORTC QLQ-C30, and EORTC QLQ-CR29; an exception to this recommendation may occur at the treatment discontinuation visit where subjects may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs are to be performed at Cycle 1 (Week 0), Cycle 2 (Week 3), Cycle 3 (Week 6), Cycle 4 (Week 9), Cycle 5 (Week 12), Cycle 7 (Week 18), and then Q9W up to a year [Cycle 10 (Week 27), Cycle 13 (Week 36), Cycle 16 (Week 45)] or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation Safety Follow-up Visit.
e. Height will be measured at Visit 1 only.
f. ECOG Performance Status and Laboratory tests for screening are to be performed within 10 days prior to the first dose of study medication. If these laboratory tests are performed within 72 hours of the first dose of study medication, then they do not need to be repeated at Cycle 1.
g. For subjects whose MSI/MMR status is unknown at the time of signing consent, the site should submit required samples to their local lab for MSI/MMR testing using an IHC or PCR-based assay prior to performing any other screening procedures. Subjects found not to be MSI-H or dMMR are deemed ineligible and should not continue with additional screening procedures (see Section 4.2.4.4).
h. For women of reproductive potential, a serum pregnancy test for screening is to be performed within 10 days prior to the first dose of study medication. If the serum pregnancy test is performed within 72 hours of the first dose of study medication, then it does not need to be repeated at Cycle 1. Thereafter, a serum pregnancy test should be performed within 72 hours prior to each cycle of study medication and 30 days post treatment.
i. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point.
j. To be performed every cycle through Cycle 6 and then every other cycle thereafter.
k. To be performed every other cycle.
l. Serum tumor marker (CEA) to be collected Q9W (±3 days), beginning at Cycle 1. Collection follows calendar days; do not adjust for cycle delays.
m. Details for the Planned Genetic Analysis Sample Collection can be found in Section 7.1.3.2.2.

Study Period:	Screening Phase		Treatment Cycles **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7

n. Whole blood samples for correlative studies (DNA and RNA) should be collected pre-dose for each of the following: Day 1, Cycle 1, Day 1, Cycle 2, Day 1, Cycle 3 and at treatment discontinuation.
o. Blood for biomarker studies (plasma and serum) should be collected pre-dose on Day 1, Cycle 1 only.
p. Submitting tumor tissue for exploratory analysis and future biomedical research (FBR) is optional and should be submitted only after the samples have been evaluated at the local site laboratory for MSI/MMR status.
q. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of randomization and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated.
r. For subjects who discontinue study medication without confirmed PD by the site per irRECIST: confirmatory tumor imaging should be performed at the time of treatment discontinuation unless previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation; tumor imaging should be continued Q9W during the post-treatment period until PD, initiation of a new anticancer therapy, withdrawal of consent, loss to follow-up, or death.

6.2 Initial Treatment Phase: SOC Chemotherapy Arm

Study Period:	Screening Phase		Treatment Cycles **(2-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures														
Informed Consent	X													
Informed Consent for Future Biomedical Research (optional)		X												
Inclusion/Exclusion Criteria		X												
Subject Identification Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X		
Survival Status[c]			<----------								---------->			X
Clinical Procedures/Assessments														
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	
ePROs (HRQoL Measures: EQ5D-3L, EORTC QLQ-C30, EORTC QLQ-CR29)[d]			X	X		X	X		X		X	X		
Full Physical Examination[e]		X									X			
Directed Physical Examination[e]			X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs		X[f]	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram		X												
ECOG Performance Status		X[g]	X	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status													X	X

Study Period:	Screening Phase		Treatment Cycles **(2-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Chemotherapy Administration			X[b]	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments														
MSI/MMR Status[h]	X													
Pregnancy Test – Serum β-HCG		X[i]	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT		X[g]												
CBC with Differential[j,k]		X[g]	X	X	X	X	X	X	X	X	X	X		
Chemistry Panel[j,k]		X[g]	X	X	X	X	X	X	X	X	X	X		
Urinalysis[j,l]		X[g]		X		X		X		X	X	X		
T3 or FT3, FT4, and TSH[j,l]		X[g]		X		X		X		X	X	X		
Serum Tumor Marker (CEA)[m]			X	X							X	X		
CENTRAL Laboratory Assessments														
Blood for Genetics (DNA)[n]			X											
Blood for Correlative Studies (DNA and RNA)[o]			X	X	X						X			
Blood for Biomarker Research (plasma and serum)[p]			X											
Tumor Tissue Collection														
Tumor Tissue[q]		X												
Efficacy Measurements														
Tumor Imaging		X	X[r]								X[s]		X[s]	

Study Period:	Screening Phase		Treatment Cycles **(2-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7

a. After the start of new anticancer therapy contacts should be made by telephone Q9W.
b. Cycle 1 treatment must be given within 3 days of randomization (however, every effort should be made to start the first treatment cycle on day of randomization). The window for each visit is ± 3 days unless otherwise noted. For Imaging ONLY: the visit window is ± 7 days and should follow calendar days and not be adjusted for cycle delays.
c. After documented disease progression, or the start of new anticancer treatment; contacts are approximately every 9 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 subjects 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 subjects who have a death event previously recorded).
d. It is strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ5D-3L, followed by EORTC QLQ-C30, and EORTC QLQ-CR29; an exception to this recommendation may occur at the treatment discontinuation visit where subjects may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs are to be performed at Cycle 1 (Week 0), Cycle 2 (Week 2), Cycle 4 (Week 6), in between Cycle 5 and Cycle 6 (Week 9), Cycle 7 (Week 12), Cycle 10 (Week 18) and then Q9W up to a year: [In between Cycle 14 and 15 (Week 27), Cycle 19 (Week 36), in between Cycle 23 and 24 (Week 45)] or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation Safety Follow-up Visit.
e. UK Only: For subjects assigned to FOLFOX based regimens only: full physical examination and directed physical examination will include neurologic and hearing examinations by the treating physician or designee.
f. Height will be measured at Visit 1 only.
g. ECOG Performance Status and Laboratory tests for screening are to be performed within 10 days prior to the first dose of study medication. If these laboratory tests are performed within 72 hours of the first dose of study medication, then they do not need to be repeated at Cycle 1.
h. For subjects whose MSI/MMR status is unknown at the time of signing consent, the site should submit required samples to their local lab for MSI/MMR testing using an IHC or PCR-based assay prior to performing any other screening procedures. Subjects found not to be MSI-H or dMMR are deemed ineligible and should not continue with additional screening procedures (see Section 4.2.4.4).
i. For women of reproductive potential, a serum pregnancy test for screening is to be performed within 10 days prior to the first dose of study medication. If the serum pregnancy test is performed within 72 hours of the first dose of study medication, then it does not need to be repeated at Cycle 1 Thereafter, a serum pregnancy test should be performed within 72 hours prior to each cycle of study medication and 30 days post treatment.
j. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point.
k. To be performed every cycle.
l. To be performed every other cycle.
m. Serum tumor marker (CEA) to be collected Q8W (±3 days), beginning at Cycle 1. Collection follows calendar days; do not adjust for cycle delays.

Study Period:	Screening Phase		Treatment Cycles **(2-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-up[a]
											At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]:	-42 to -29	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7

n. Details for the Planned Genetic Analysis Sample Collection can be found in Section 7.1.3.2.2.
o. Whole blood samples for correlative studies (DNA and RNA) should be collected pre-dose for each of the following: Day 1, Cycle 1, Day 1, Cycle 2, Day 1, Cycle 3 and at treatment discontinuation.
p. Blood for biomarker studies (plasma and serum) should be collected pre-dose on Day 1, Cycle 1 only.
q. Submitting tumor tissue for exploratory analysis and FBR is optional and should be submitted only after the samples have been evaluated at the local site laboratory for MSI/MMR status.
r. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of randomization and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated.
s. For subjects who discontinue study medication without confirmed PD by the site per RECIST 1.1: confirmatory tumor imaging should be performed at the time of treatment discontinuation unless previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation; tumor imaging should be continued Q9W during the post-treatment period until PD, initiation of a new anticancer therapy, withdrawal of consent, loss to follow-up, or death.

6.3 Second Course Treatment Phase: Pembrolizumab (MK-3475) Arm and SOC Chemotherapy Arm following Crossover

Study Period:	Treatment Period **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-Up[a]
									At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures												
Eligibility Criteria	X											
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Survival Status[c]	<----------										---------->	X
Clinical Procedures/Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X								X			
Directed Physical Examination		X	X	X	X	X	X	X				
Weight, and Vital Signs	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X			
Post-study anticancer Therapy Status											X	X
Pembrolizumab (MK-3475) Administration	X	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments												
Pregnancy Test – Serum β-HCG[d]	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT	X[f]											
CBC with Differential[e,g]	X [f]	X	X	X	X	X		X	X	X		
Chemistry Panel[e,g]	X [f]	X	X	X	X	X		X	X	X		

Study Period:	Treatment Period **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-Up[a]
									At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Urinalysis[e,h]	X [f]		X		X		X		X	X		
T3 or FT3, FT4, and TSH[e,h]	X [f]		X		X		X		X	X		
Serum Tumor Marker (CEA)[i]	X			X			X					
Efficacy Measurements												
Tumor Imaging	X[j]			X			X		X[k]		X[k]	

a. After the start of new anticancer treatment or PD the subject should be contacted by telephone Q9W.
b. The window for each visit is ± 3 days unless otherwise noted. For Imaging ONLY: the visit window is ± 7 days and should follow calendar days and not be adjusted for cycle delays.
c. After documented disease progression, or the start of new anticancer treatment; contacts are approximately every 9 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 subjects 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 subjects who have a death event previously recorded).
d. For women of reproductive potential, a serum pregnancy test for screening is to be performed within 10 days prior to the first dose of study medication. If the serum pregnancy test is performed within 72 hours of the first dose of study medication, then it does not need to be repeated at Cycle 1. Thereafter, a serum pregnancy test should be performed within 72 hours prior to each cycle of retreatment with pembrolizumab (MK-3475) and 30 days post treatment.
e. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point.
f. Laboratory tests for determining eligibility are to be performed within 10 days prior to the first retreatment dose of pembrolizumab (MK-3475). If these laboratory tests are performed within 72 hours of the first dose of study medication, then they do not need to be repeated at Cycle 1.
g. Complete blood count (CBC) and Chemistry to be performed every cycle through Cycle 6 and then every other cycle thereafter.
h. To be performed every other cycle.
i. Serum tumor marker (CEA) to be collected Q9W (±3 days), beginning at Cycle 1. Collection follows calendar days; do not adjust for cycle delays.
j. Tumor imaging should be performed within 28 days prior to restarting treatment with pembrolizumab (MK-3475) and continue to be performed Q9W (63 ± 7 days) calculated from the first dose of retreatment, or more frequently if clinically indicated.
k. For subjects who discontinue study medication without confirmed PD by the site per irRECIST: confirmatory tumor imaging should be performed at the time of treatment discontinuation unless previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation; tumor imaging should be continued Q9W during the post-treatment period until PD, initiation of a new anticancer therapy, withdrawal of consent, loss to follow-up, or death.

6.4 Crossover Phase: SOC Chemotherapy Arm

Crossover subjects from SOC chemotherapy must have confirmation of PD per RECIST 1.1 by blinded central imaging vendor and be qualified for Crossover Phase.

Study Period:	Treatment Period **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-Up[a]
									At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures												
Eligibility Criteria	X											
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Survival Status[c]	<----------										---------->	X
Clinical Procedures/Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X								X			
Directed Physical Examination		X	X	X	X	X	X	X				
Weight, and Vital Signs	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X			
Post-study anticancer Therapy Status											X	X
Pembrolizumab (MK-3475) Administration	X	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments												
Pregnancy Test – Serum β-HCG[d]	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT	X[f]											

Study Period:	Treatment Period **(3-Week Cycles)**								End of Treatment	Post-treatment		
Treatment Cycle/Title:	1	2	3	4	5	6	7	8 and beyond	Discon	Safety Follow-up	Follow-Up Visits	Survival Follow-Up[a]
									At time of discon	30 days post-discon	Q9W post-discon	Q9W
Scheduling Window (Days)[b]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
CBC with Differential[e,g]	X[f]	X	X	X	X	X		X	X	X		
Chemistry Panel[e,g]	X[f]	X	X	X	X	X		X	X	X		
Urinalysis[e,h]	X[f]		X		X		X		X	X		
T3 or FT3, FT4, and TSH[e,h]	X[f]		X		X		X		X	X		
Serum Tumor Marker (CEA)[i]	X			X			X					
Efficacy Measurements												
Tumor Imaging	X[j]			X			X		X[k]		X[k]	

a. After the start of new anticancer treatment or PD the subject should be contacted by telephone Q9W.
b. The window for each visit is ± 3 days unless otherwise noted. For Imaging ONLY: the visit window is ± 7 days and should follow calendar days and not be adjusted for cycle delays.
c. After documented disease progression, or the start of new anticancer treatment; contacts are approximately every 9 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 subjects 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 subjects who have a death event previously recorded).
d. For women of reproductive potential, a serum pregnancy test for screening is to be performed within 10 days prior to the first dose of study medication. If the serum pregnancy test is performed within 72 hours of the first dose of study medication, then it does not need to be repeated at Cycle 1. Thereafter, a serum pregnancy test should be performed within 72 hours prior to each cycle of retreatment with pembrolizumab (MK-3475) and 30 days post treatment.
e. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point.
f. Laboratory tests for determining eligibility are to be performed within 10 days prior to the first retreatment dose of pembrolizumab (MK-3475). If these laboratory tests are performed within 72 hours of the first dose of study medication, then they do not need to be repeated at Cycle 1.
g. Complete blood count (CBC) and Chemistry to be performed every cycle through Cycle 6 and then every other cycle thereafter.
h. To be performed every other cycle.
i. Serum tumor marker (CEA) to be collected Q9W (±3 days), beginning at Cycle 1. Collection follows calendar days; do not adjust for cycle delays.
j. Tumor imaging should be performed within 28 days prior to restarting treatment with pembrolizumab (MK-3475) and continue to be performed Q9W (63 ± 7 days) calculated from the first dose of retreatment, or more frequently if clinically indicated.
k. For subjects who discontinue study medication without confirmed PD by the site per irRECIST: confirmatory tumor imaging should be performed at the time of treatment discontinuation unless previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation; tumor imaging should be continued Q9W during the post-treatment period until PD, initiation of a new anticancer therapy, withdrawal of consent, loss to follow-up, or death.

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.

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 study.

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. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Disease details regarding the subject's CRC will be recorded separately and not listed as medical history.

Please note that if the subject has lost at least 15 lbs. (6.8 kg.) over the three months prior to screening, "weight loss" should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

7.1.1.5 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's CRC.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days of first dose of study medication. Prior anticancer treatment for CRC be recorded separately and not listed as a prior medication.

7.1.1.6.1.1 Prior Treatment Details for Colorectal Carcinoma

The investigator or qualified designee will review all prior anticancer treatments including systemic treatments, radiation and surgeries.

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the study from the date of first dose of study medication through the Safety Follow-up visit. In addition, new medications started during the Second Course/Crossover Phase through the Second Course/Crossover Safety Follow-up Visit should be recorded.

All medications related to reportable SAEs should be recorded as defined in Section 7.2.

7.1.1.7 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 7.1.6.1.

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated 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.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.9 Trial Compliance (Medication/Diet/Activity/Other)

Dosing interruptions are permitted with Sponsor consultation in the case of medical/surgical events or logistical reasons not related to study medication (eg, elective surgery [including surgery for curative intent], unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study medication within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. As such, there shall be a maximum of 6 weeks between doses of pembrolizumab and a maximum of 5 weeks between doses of SOC. Scheduled dosing interruption of longer than the aforementioned requires written Sponsor approval.

Administration of study medication will be witnessed by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures.

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 Study Flow Chart and more frequently if clinically indicated. Adverse events 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 study medication.

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

7.1.2.2 Electronic Subject Reported Outcomes (ePROs)

The EuroQoL EQ5D-3L, EORTC QLQ-C30, and EORTC QLQ-CR29 questionnaires will be administered by trained study site personnel and completed electronically by subjects. It is strongly recommended that the electronic EORTC QLQ-C30, EORTC QLQ-CR29 and EuroQoL EQ5D-3L are completed by the subject prior to drug administration, adverse event evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit. ePROs will be administrated in the following order: EuroQoL EQ5D-3L first, then EORTC QLQ-C30, and lastly the EORTC QLQ-CR29 at the time points specified in the Study Flow Chart.

7.1.2.3 Physical Exam

7.1.2.3.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams should be performed as specified in the Study Flow Chart – Section 6.0. After the first dose of study medication new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Study Flow Chart – Section 6.0, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing ±3 days of Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Height, Weight, and Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of study medication, and at treatment discontinuation as specified in the Study Flow Chart – Section 6.0.

Vital signs should include temperature, pulse, respiratory rate, blood pressure, and weight. Height will be measured at screening only.

7.1.2.5 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed one time during screening using local standard procedures. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG Performance Status (see Section 12.5) at screening, prior to dosing ±3 days of Day 1 of each treatment cycle, and at discontinuation of study medication as specified in the Study Flow Chart – Section 6.0.

7.1.2.7 Post-study Anticancer Therapy Status

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of study medication. If a subject initiates a new anticancer therapy within 30 days after the last dose of study medication, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy.

Once new anticancer therapy has been initiated the subject will move into survival follow-up.

7.1.3 Laboratory Procedures/Assessments

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

Refer to the Study Flow Chart – Section 6.0 for the schedule of laboratory assessments.

7.1.3.1 Local Laboratory Assessments

7.1.3.1.1 Hematology, Chemistry, Urinalysis, and Other Labs

All required laboratory tests are specified in Table 8.

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Specific gravity	Thyroid stimulating hormone (TSH)
Hemoglobin	Alkaline phosphatase	Microscopic exam, if abnormal results are noted	Serum β-human chorionic gonadotropin (β-hCG)[a]
Platelet count	Lactate dehydrogenase (LDH)	Protein	Serum tumor markers (CEA)
White blood cell (WBC) count (total and differential)[b]	ALT	Glucose	Total triiodothyronine (T3) or Free T3 (FT3)[c]
Absolute neutrophil count [d]	AST	Blood	Free thyroxine (FT4)
Absolute lymphocyte count [d]	Bicarbonate or Carbon dioxide[e]		PT(INR)
	Calcium		aPTT
	Chloride		Blood for correlative studies
	Creatinine		PK
	Glucose		Anti-pembrolizumab (MK-3475) antibodies
	Potassium		Blood for Genetics
	Sodium		Blood for Biomarkers
	Total bilirubin		
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen/Urea[f]		

a. Perform on women of childbearing potential only. Serum pregnancy test is required.
b. Absolute results will be requested for the clinical database.
c. T3 is preferred; if not available free T3 may be tested. If the local laboratory is unable to perform either of these tests the site should submit the sample to the central laboratory for testing; details are provided in the Central Laboratory Manual.
d. Results should be calculated per local standard of practice.
e. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
f. Blood Urea Nitrogen is preferred; if not available urea may be tested.

Laboratory tests for screening should be performed within 10 days prior to the first dose of study medication. Subjects eligible for retreatment with pembrolizumab (MK-3475) should have lab test performed within 10 days prior to the first dose of study medication in the Second Course Phase. After Cycle 1, in both the Initial Treatment Phase for pembrolizumab (MK-3475) or SOC chemotherapy, and the Second Course Phase/Crossover with pembrolizumab (MK-3475) treatment, pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing.

Laboratory test results (with the exception of thyroid tests and CEA) must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study medication. Unresolved abnormal labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

7.1.3.1.2 Serum β-hCG

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours prior to each cycle of study medication and 30 days post treatment and must be excluded in the event of a positive or borderline-positive test result. Serum β -HCG test is required.

7.1.3.2 Central Laboratory Assessments

7.1.3.2.1 Pharmacokinetic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 3, each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 3 may be stored only at this time. Analysis will be performed if required.

7.1.3.2.2 Planned Genetic Analysis Sample Collection

A sample should be drawn at the Cycle 1 visit 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 future biomedical research if the subject signs the Future Biomedical Research consent. If the planned genetic analysis is not approved, but Future Biomedical Research is approved and consent is given, this sample will be collected for the purpose of Future Biomedical Research.

7.1.3.2.3 Blood for Correlative and Biomarker Studies

Blood for correlative biomarker studies (RNA and DNA) should be collected pre-dose for each of the following: Day 1, Cycle 1, Day 1, Cycle 2, Day 1, Cycle 3 and at treatment discontinuation; blood for biomarker studies (plasma and serum) should be collected pre-dose on Day 1, Cycle 1 only. Detailed instructions for each sample are provided in the Procedures Manual.

If the sample is collected, leftover DNA, RNA, plasma and serum will be stored for future biomedical research if the subject signs the Future Biomedical Research consent.

7.1.3.2.3.1 Tumor Tissue for Exploratory Analyses

Submitting tumor tissue is optional in this study. The sponsor may use tumor tissue for exploratory analyses to identify factors important for pembrolizumab (MK-3475) therapy (See Section 4.2.4.5). If the subject signs the Future Biomedical Research (FBR) consent,

any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

7.1.3.3 Future Biomedical Research Sample Collection

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

(DNA) for future research.

- Leftover tumor tissue
- Leftover DNA, RNA, plasma and serum

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and RECIST Assessment

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 computed tomography (CT, strongly preferred). MRI should be used when 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 study to optimize the visualization of existing and new tumor burden.

Imaging should include the chest, abdomen, and pelvis.

Local site investigator/radiology assessment based on RECIST 1.1 will be used to determine subject eligibility. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, if the site obtains additional unscheduled imaging (including other modalities) that is related to disease progression, response, or adverse events, all of these additional imaging must be submitted to the central imaging vendor.

The central imaging vendor will verify PD following local site investigator-assessed 1st radiologic evidence of PD. Expedited verification of radiologic PD by the central imaging vendor will be communicated to the study site and sponsor (See Section 7.1.4.6).

7.1.4.2 Initial Tumor Imaging

Tumor imaging at screening must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted to the central imaging vendor for retrospective confirmation of eligibility.

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

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT if CT was used at prior imaging for at least four weeks prior to the first dose of study medication; also, any neurologic symptoms must have returned to baseline, have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to study initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.4.3 On Study Tumor Imaging

During the Initial Treatment Phase, the first on-study imaging assessment will be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor imaging will be performed Q9W (63 days ±7 days) or more frequently if clinically indicated. Imaging timing will follow calendar days and should not be adjusted for delays in cycle starts or any dose interruptions. Subjects who undergo surgical resection with curative intent while on study should resume imaging postoperatively when clinically possible to maintain the Q9W imaging schedule.

Imaging should continue to be performed until 1) radiologic disease progression per RECIST 1.1 (see Figure 8), 2) the start of new anticancer treatment, 3) withdrawal of consent, 4) death, or 5) notification by the Sponsor.

For all subjects, per RECIST 1.1, partial or complete response (PR or CR) should be confirmed by a repeat tumor imaging assessment. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging Q9W, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per irRECIST (Section 7.1.4.6), disease progression on subjects treated with pembrolizumab should be confirmed locally by the site at least 4 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.4.6. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects with confirmed disease progression, as assessed by the site, will discontinue study medication. Exceptions are detailed in Section 7.1.4.6.

For subjects who restart treatment in the Second Course Phase or subjects who crossover to pembrolizumab (MK-3475) from SOC arm, tumor imaging must be performed within 28 days prior to treatment with pembrolizumab (MK-3475). The first Second Course/Crossover Phase imaging assessment should be performed at 9 weeks (63 days

±7 days) after the restart of treatment. Subsequent tumor imaging should be performed Q9W or more frequently if clinically indicated. If tumor imaging shows initial PD per RECIST 1.1, 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.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD in clinically stable subjects. Additional irRECIST detail is described in Section 7.1.2.5.6.

All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, if the site obtains additional imaging, including other modalities, that are obtained at an unscheduled time point to determine if the subject has progressed as well as imaging obtained for other reasons but captures radiologic progression, all of these imaging scans must be sent to the central imaging vendor.

7.1.4.4 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue study medication, 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 is not mandatory. In subjects who discontinue study medication due to documented disease progression (PD or irPD for subjects managed under irRECIST), this is the final required tumor imaging if the Investigator elects not to implement irRECIST.

In subjects who discontinue study medication without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (Q9W) until the start of new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

7.1.4.5 RECIST 1.1 Assessment of Disease

Evaluation of tumor response by RECIST 1.1 per the central imaging vendor is the basis for efficacy assessment in this study.

Figure 8 illustrates the imaging flow after 1st radiologic evidence of PD per RECIST 1.1.

7.1.4.6 Immune-related RECIST (irRECIST) Assessment of Disease (for subjects on Pembrolizumab (MK-3475) ONLY)

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions while subjects are receiving pembrolizumab (MK-3475). Treatment efficacy based on irRECIST as assessed by central imaging vendor review will be evaluated

retrospectively and is an exploratory objective for this study. See Table 9 for management of subjects per irRECIST.

This clinical judgment decision by the site should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. 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 (eg, cord compression) requiring urgent alternative medical intervention

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s). Confirmation of PD at repeat imaging is defined by occurrence of ANY of the following conditions:

- Tumor burden 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 progression since last evaluation

ALL of the following conditions must be met in order for PD NOT to be confirmed at repeat imaging:

- Tumor burden 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 progression since last evaluation

Additional details about irRECIST are referenced in the Merck TIP Sheet for RECIST 1.1 and irRECIST.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment.

Table 9 Imaging and Treatment after First Radiologic Evidence of PD for Subjects Receiving Pembrolizumab (MK-3475) (management per irRECIST)

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1 (1)	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study medication at the investigator's discretion while awaiting confirmatory tumor imaging.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (2)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study medication at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study medication if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

(1) PD must be verified by the central imaging vendor for subjects who experience 1st PD while receiving pembrolizumab (MK-3475) in the Initial Treatment Phase. Subjects who cross over from chemotherapy (control) arm, and who experience 1st PD on pembrolizumab (MK-3475) will have PD verified by the local site/investigator.

(2) If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor. Follow-up scans will then be performed Q9W (63 ± 7 days) or earlier as clinically indicated. (France only: does not apply.)

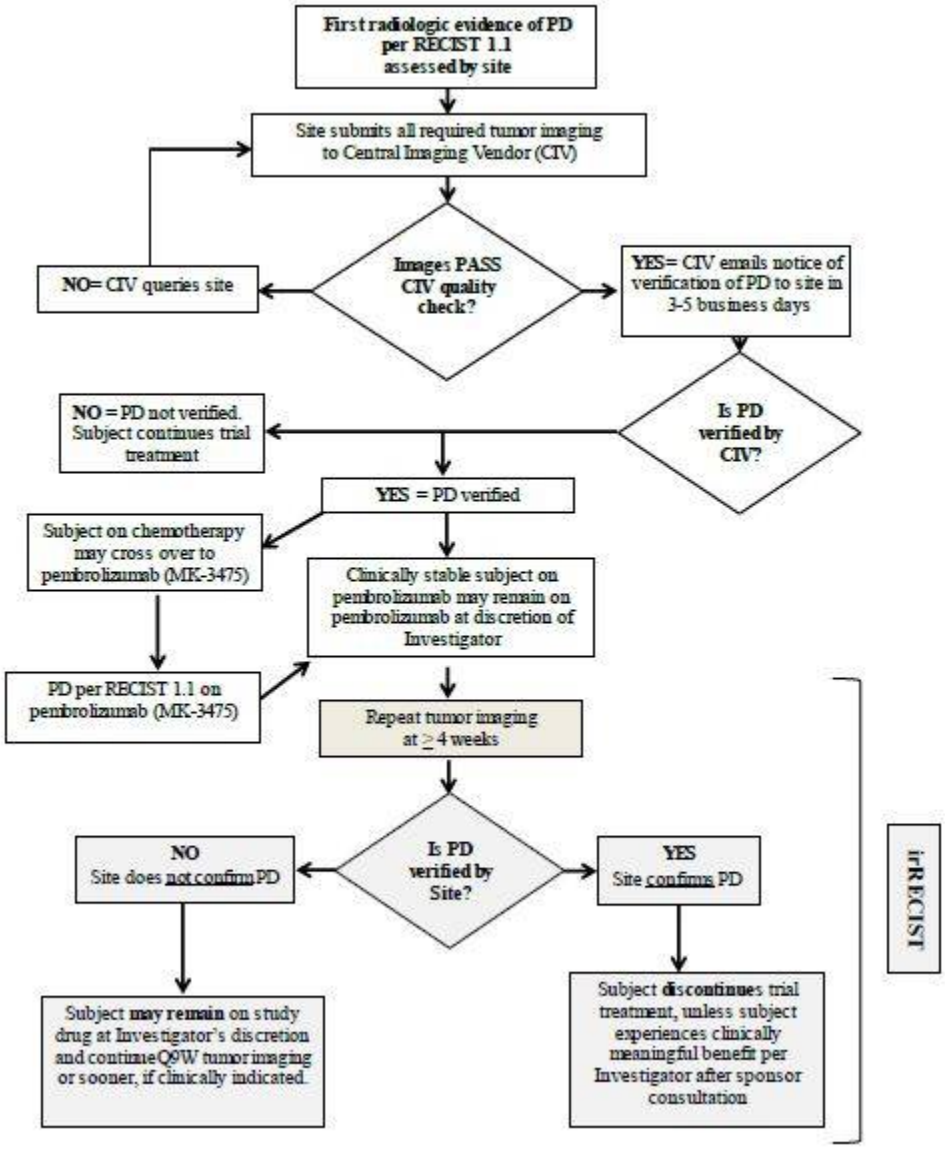


Figure 8 Imaging and Treatment after First Radiologic Evidence of PD

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment 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 final study 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.

7.1.5.1.1 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.

7.1.5.2 Blinding/Unblinding

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

7.1.5.3 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 study assessments
- Imaging equipment – as required for study objectives

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

7.1.6 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.

7.1.6.1 Screening

Approximately 42 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

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. Once MSI/MMR status is determined and a subject is considered eligible, the remaining screening procedures are to be completed within 28 days prior to randomization except for the following:

- Laboratory tests and ECOG performance status are to be performed within 10 days prior to treatment initiation.

- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of study medication.

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 repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects may not rescreen more than 1 time without consulting with the sponsor. Subjects who are rescreened will retain their original screening number.

7.1.6.2 Treatment Period

Visit requirements are outlined in the Study Flow Chart (Section 6.0). Specific procedure-related details are provided above in the Study Procedures (Section 7.1)

7.1.6.3 Second Course Phase for Subjects Receiving Pembrolizumab (MK-3475) in the Initial Treatment Phase or Crossover from SOC Treatment Phase

Subjects who stop pembrolizumab (MK-3475) with SD or better may be eligible for up to 17 additional study medications (approximately 1 year) if they progress after stopping study medications. Retreatment with pembrolizumab (MK-3475) is termed the Second Course Phase and is only available if the subject meets the following conditions:

- **Either**
    - Stopped initial/crossover treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
        - Was treated with at least 8 study medications (approximately 6 months) with pembrolizumab (MK-3475) before discontinuing therapy
        - Received at least 2 treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab (MK-3475) after 35 study medications (approximately 2 years) for reasons other than disease progression or intolerability

- **AND**

  - Experienced an investigator-determined radiographic disease progression (which must also be verified centrally) after stopping their initial/crossover treatment with pembrolizumab (MK-3475). If a subject is unstable as a result of a new or progressing brain metastasis, the subject will not be eligible for the Second Course Treatment Phase, unless stability per exclusion criterion # 6 is satisfied after the management of the new/progressing brain metastasis

  - Did not receive any anticancer treatment since the last dose of pembrolizumab (MK-3475)

  - Has a performance status of 0 or 1 on the ECOG Performance Scale

  - Demonstrates adequate organ function as detailed in Table 4.

  - Female subject of childbearing potential should have a negative serum test within 72 hours prior to receiving retreatment with pembrolizumab (MK-3475).

  - Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab (MK-3475) (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

  - Male subject should agree to use an adequate method of contraception starting with the first dose through 120 days after the last dose of pembrolizumab (MK-3475).

  - 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 study or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who enter the Second Course Phase will be retreated at the same dose frequency as when they last received pembrolizumab (MK-3475). Pembrolizumab (MK-3475) may be administered for up to an additional 17 study medications (approximately 1 year).

Visit requirements for the Second Course Phase are outlined in the Second Course Phase Study Flow Chart (Section 6.3).

7.1.6.4 Crossover Phase for Subjects in the Chemotherapy Arm with Documented Disease Progression

Subjects on the SOC arm with documented disease progression following chemotherapy may be eligible to participate in the crossover arm of this study. Crossover subjects may be treated with up to 35 pembrolizumab (MK-3475) treatment cycles. Subjects who permanently discontinue chemotherapy due to an adverse event (see below for details) or withdrawal of consent, or for any reason other than progressive disease, will not be eligible for crossover. Surgical subjects who progress post-operatively are eligible to receive pembrolizumab (MK-3475) in the Crossover Phase with up to 35 administrations (approximately 2 years) of pembrolizumab (MK-3475).

If SOC is delayed due to surgery or an AE resulting in >5 weeks between doses of SOC, and progression of disease occurs during the delay, the subject may qualify for crossover if he or she fulfill all criteria described below and after consultation with the Sponsor.

Subjects on the SOC arm who have entered the Follow-up Phase (discontinued treatment due to a reason other than disease progression) are not allowed to move to the crossover phase, as they do not meet the criteria outlined above.

Crossover subjects may not initiate treatment with pembrolizumab (MK-3475) any earlier than 30 days after their last dose of chemotherapy (washout period) regardless of the time of progression. Subjects will need to complete the discontinuation visit. Of note, the 30 day safety follow-up visit may occur on the same day as the first dose of pembrolizumab (MK-3475) in the Crossover Phase. Subjects may not initiate therapy with pembrolizumab (MK-3475) until PD has been verified by central imaging vendor and meeting eligibility criteria.

Crossover is optional and is at the discretion of the investigator (with the Sponsor's agreement). Imaging must be completed to establish a new baseline for the Crossover Phase.

Subject must meet the following criteria for crossover:

- Has progressive disease per RECIST 1.1 verified by central imaging vendor. If a subject is unstable as a result of a new or progressing brain metastasis, the subject will not be eligible for crossover, unless stability per exclusion criterion # 6 is satisfied after the management of the new/progressing brain metastasis.
- Did not receive any other anticancer treatment since the last dose of study chemotherapy
- Chemotherapy and bevacizumab/cetuximab induced adverse events must have improved to CTCAE (version 4.0) ≤ Grade 1. Exceptions may be considered following Sponsor consultation.
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Table 4.
- Female subject of childbearing potential should have a negative serum test within 72 hours prior to receiving treatment with pembrolizumab (MK-3475).

- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of pembrolizumab (MK-3475) (Reference Section 5.7.2) or through 180 days after the last dose of chemotherapy, whichever later. Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for >1 year.

- Male subject should agree to use an adequate method of contraception starting with the first dose through 120 days after the last dose of pembrolizumab (MK-3475), or through 180 days after the last dose of chemotherapy, whichever later.

- Does not have evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the study or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

- Has no major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to first dose of pembrolizumab (MK-3475).

- For subjects who stopped Oxaliplatin to prevent neuropathy (see section 5.2.1.2), if progression occurs after Oxaliplatin is restarted per Section 5.2.1.2, Dose Modification - SOC arm, crossover is allowed if the patient has no neuropathy or other treatment induced AE with grade >1. If progression occurs during the 12 cycles of 5FU/leucovorin without Oxaliplatin and the patient has no neuropathy or other treatment induced AE with grade >1, crossover is also allowed. If Oxaliplatin is not restarted after 12 cycles of 5FU/leucovorin without evidence of neuropathy, and the subject has progression, crossover is not allowed.

Subjects who crossover and then achieve a CR per RECIST 1.1 have the option to hold pembrolizumab (MK-3475) at the discretion of the investigator. **See Section 7.1.4.6 for management per irRECIST**. Subjects who stop pembrolizumab (MK-3475) in the crossover phase with SD or better may be eligible for up to 17 additional study medications (approximately 1 year) in the Second Course Phase if they progress after stopping study medication. Additional details are provided in Second Course Phase Section 7.1.6.3. Subjects who permanently discontinue the Crossover Phase will follow the same Survival Follow-up assessments outlined Section 7.1.6.5.3. Visit requirements for the Crossover Phase are outlined in the Crossover Phase Study Flow Chart (Section 6.4).

7.1.6.5 Post Treatment Visits

7.1.6.5.1 Safety Follow-up Visits

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study medication or before the initiation of a new anticancer treatment, whichever comes first. Subjects who are eligible for retreatment/crossover with pembrolizumab (MK-3475) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment/Crossover Phase.

7.1.6.5.2 Follow-up Visits

Subjects who discontinue study medication for reasons other than disease progression (including subjects who have received the maximum 35 pembrolizumab treatments) will move into the Follow-up Phase and should be assessed Q9W by radiologic imaging to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study (or if the subject begins retreatment with pembrolizumab as detailed in Sections 7.1.6.3). Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab (MK-3475) according to the criteria in Section 7.1.6.3 will move from the Follow-up Phase to the Second Course Phase when they experience centrally confirmed disease progression. Details are provided in the Trial Flow Chart (Section 6) for retreatment with pembrolizumab.

7.1.6.5.3 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 Q9W to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.6.6 Survival Status

Details regarding Survival Follow-up are outlined in Section 7.1.6.5.3.

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 subjects 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 subjects 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 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

In this study, an overdose is any dose higher than ≥1000 mg (5 times the protocol defined dose) of pembrolizumab (MK-3475). No specific information is available on the treatment of over dose of pembrolizumab (MK-3475). In the event of overdose, study medication should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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) that occurs during the trial.

Pregnancies and lactations 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. Pregnancies and lactations 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 by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious 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 10 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:

- 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.
- 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.

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 study. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as an 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 v4.0. 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.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 10 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.

7.2.6 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the Executive Oversight Committee (EOC) regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

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 the primary and/or 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 statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. There will be a separate PK analysis plan, if required (see Section 7.1.3.2.1), as well as a biomarker analysis plan. 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 through 8.12.

Study Design Overview	A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)
Treatment Assignment	Approximately 300 subjects will be randomized in a 1:1 ratio to receive pembrolizumab (MK-3475) or standard of care (SOC). This is an open-label study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. Progression-free Survival (PFS) per RECIST 1.1 by central imaging vendor 2. Overall Survival (OS)
Secondary Endpoint	Overall Response Rate (ORR)
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab (MK-3475) to SOC on PFS and OS using a Log-rank test. Estimation of the hazard ratio will be done using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	[redacted] [redacted] The between-treatment difference will be analyzed using the Miettinen and Nurminen method. In the primary safety comparison between pembrolizumab (MK-3475) and SOC, subjects who crossover to pembrolizumab (MK-3475) are censored at time of crossover (ie, AEs occurring during treatment with pembrolizumab (MK-3475) are excluded for control-arm subjects). An exploratory safety analysis will be conducted for the crossover population including all safety events starting from the date of randomization.
Interim Analysis	Two interim analyses will be performed. Results will be reviewed by an external DMC. Details are provided in Section 8.7. IA1: to be performed after 1) approximately 162 PFS events have occurred; and 2) 6 months after last subject randomized Primary purpose: interim PFS and interim OS analysis IA2: to be performed after approximately 209 PFS events have occurred or 24 months after last subject randomized, whichever occurs first Primary purpose: final PFS and interim OS analysis
Multiplicity	The overall type-I error over the primary hypotheses (related to PFS and OS) and the secondary hypothesis (related to ORR) is strongly controlled at 2.5% (one-sided), [redacted] [redacted]

Sample Size and Power	The planned sample size is approximately 300 subjects. The final analysis will be performed after approximately 190 OS events have occurred or 12 months after Interim Analysis 2, whichever occurs first (see Section 8.9). For PFS, the study has around 98% power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 1.25% alpha-level, [redacted] For OS, the study has 85% power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 1.25% alpha-level, [redacted] However, due to the anticipated high crossover rate, the actual power could be substantially lower.

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.

The Sponsor will generate the randomized allocation schedule(s) for study medication assignment for this protocol, and the randomization will be implemented in IVRS. Although the study is open label, analyses or summaries generated by randomized treatment assignment, and/or actual treatment received will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

The eDMC will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the SPONSOR. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment-level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

- **Progression-free survival (PFS) – RECIST 1.1 assessed by central imaging vendor**

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

- **Overall Survival**

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date of last known contact.

Secondary

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

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

Exploratory

- **Progression-free survival 2** (PFS2)

Progression-free survival 2 (PFS2) is defined as the time from randomization to disease progression on the next line of therapy, or death from any cause, whichever first.

- **Progression-free survival (PFS) – irRECIST assessed by central imaging vendor**

Progression-free-survival (PFS) is defined as the time from randomization to the first confirmed disease progression or death due to any cause, whichever occurs first.

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

For subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of first documented disease progression or death.

- **Surgical conversion rate**

The surgical conversion rate is the rate of subjects who become eligible and undergo resection with curative intent as a result of study therapy.

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized. ITT population consists of all randomized subjects whether or not treatment was administered. Any subject who receives a treatment randomization number will be considered to have been randomized.

[redacted]

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 randomized subjects who received at least one dose of study medication. Subjects will be included in the treatment group corresponding to the study medication they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study medication for the entire treatment period will be included in the treatment group corresponding to the study medication actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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

8.6 Statistical Methods

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.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity.

8.6.1.1 Progression-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the log-rank test and the P-value will be provided. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the Cox model with Efron's method of tie handling and with a single treatment covariate will be reported.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by central imaging vendor, regardless of discontinuation of study drug. Death is always considered as a confirmed PD

event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

CCI

CCI

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
CCI	CCI	CCI	CCI
CCI			

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for PFS will be plotted for the comparison between pembrolizumab (MK-3475) and the SOC arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies (eg, using Restricted Mean Survival Time (RMST) method, parametric method etc.).

Further details of sensitivity analyses will be described in the supplemental SAP.

8.6.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the log-rank test. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% confidence interval from the Cox model with a single treatment covariate will be reported.

Since subjects in the SOC arm are allowed to switch to the pembrolizumab (MK-3475) treatment after progressive disease, adjustment for the effect of crossover on OS will be performed as a sensitivity analysis based on recognized methods, eg, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [40], two-stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods. An additional OS sensitivity analysis will be performed with survival dates censored at the start of crossover treatment or the start of first subsequent immune checkpoint inhibitor treatment, whichever occurs first.

Further details of sensitivity analyses will be described in the supplemental SAP.

8.6.1.3 Overall Response Rate (ORR)

The Miettinen and Nurminen method will be used for comparison of the Overall Response Rate between the treatment arms. The point estimate, 95% Confidence Interval for the difference in response rate between the pembrolizumab arm and the control arm will be provided. Subjects without response data will be counted as non-responders. Table 12 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, and interim analyses is described in Section 8.7 Interim Analyses and in Section 8.8 Multiplicity.

cci [redacted]

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints			
cci [redacted]	cci [redacted]	cci [redacted]	cci [redacted]
Secondary Endpoint			
cci [redacted]			

8.6.2 Statistical Methods for Safety Analyses

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

Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA and grouped system organ class. AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Tiered Approach

cci [redacted]

In the primary safety comparison between pembrolizumab (MK-3475) and SOC, subjects who crossover to pembrolizumab (MK-3475) are censored at time of crossover (ie, AEs occurring during treatment with pembrolizumab (MK-3475) are excluded for control-arm subjects). An exploratory safety analysis will be conducted for the crossover population including all safety events starting from the date of randomization.

[redacted]

[redacted]

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age), 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 Analyses

The study has 2 planned interim analyses. Results will be reviewed by an eDMC.

For the PFS and OS hypotheses, Lan-DeMets O'Brien-Fleming alpha spending function will be used to construct group sequential boundaries to control the Type-I error. For PFS analysis, the extended graphical method (Anderson et al, unpublished data, 2018) is used. This method spends alpha as a function of the minimum of the actual event information fraction and the expected event information fraction. [redacted]

[redacted]

[redacted]

Analysis	Criteria for Conduct of Analysis	Endpoint	p-value†	Approximate Efficacy Boundary (HR)†
[redacted]				

8.8 Multiplicity

The overall type I error over the primary endpoints (PFS and OS) and the secondary endpoint (ORR) is strongly controlled at 2.5% (one-sided), [redacted]

[redacted]

Figure 9 Multiplicity Strategy

8.9 Sample Size and Power Calculations

The primary objective of this study is to evaluate the efficacy of Pembrolizumab (MK-3475) compared to the standard of care with respect to PFS and OS for subjects with Microsatellite Instability-High or Mismatch Repair Deficient Stage IV Colorectal Carcinoma. Approximately 300 subjects will be enrolled.

PFS analysis: The final PFS analysis will be performed at the time of Interim Analysis 2 when approximately 209 PFS events have occurred or 24 months after last subject randomized, whichever occurs first. With 209 PFS events, the study has ~98% power for PFS at the 1.25% (one-sided) significance level. If fewer than 209 events are observed 24 months after last subject randomized, the power will be lower; for example, if 192 events are observed, then the study has 97% power for PFS.

OS analysis: The final OS analysis will be performed after approximately 190 OS events have occurred or 12 months after Interim Analysis 2, whichever occurs first. With 190 OS events, the study has ~85% power for OS vs. SOC) of 0.62 at the 1.25% (one-sided) significance level. If fewer than 190 events are observed 12 months after Interim Analysis 2, the power will be lower;

[redacted]

ORR analysis: ORR is a secondary endpoint. The ORR analysis will be conducted when either PFS or OS null hypothesis is rejected. The study has 92% power to demonstrate the superiority of Pembrolizumab (MK-3475) over SOC at one-sided 2.5% α-level, [redacted]

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for the 2 primary endpoints will be estimated and plotted within each category of the following classification variables:

- Age category (≤70 vs. >70 years)
- Geographic region (Asia vs. Western Europe/North America vs. Rest of World)
- Hepatic or pulmonary metastases vs other metastases
- Recurrent vs newly diagnosed stage IV CRC
- BRAF wild-type vs. BRAF V600E
- Site of primary tumor (right vs. left)
- Surgical vs non-surgical subjects, where surgical subjects are those who have surgery with curative intent

8.11 Compliance (Medication Adherence)

Drug accountability data for study medication will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

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 15.

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 15 Product Descriptions

Product Name & Potency	Dosage Form	Source / Additional Information
Pembrolizumab, (MK-3475) 25 mg/mL, 4 mL	Injection	Provided centrally by the SPONSOR
Oxaliplatin, 5 mg/mL	Injection	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Fluorouracil, 50 mg/mL	Injection	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Calcium leucovorin, 10 mg/mL	Injection	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Irinotecan, 20 mg/mL	Injection	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Bevacizumab, 25 mg/mL	Injection	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Cetuximab, 5 mg/mL	Injection	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

All other supplies not indicated in Table 15 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible to record 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 vials for every 3-week dosing for MK-3475 and every 2 weeks for the standard of care drugs. The standard of care supplies may or may not be kitted, depending on the commercial presentation.

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 member 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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 patient 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 (ie, 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

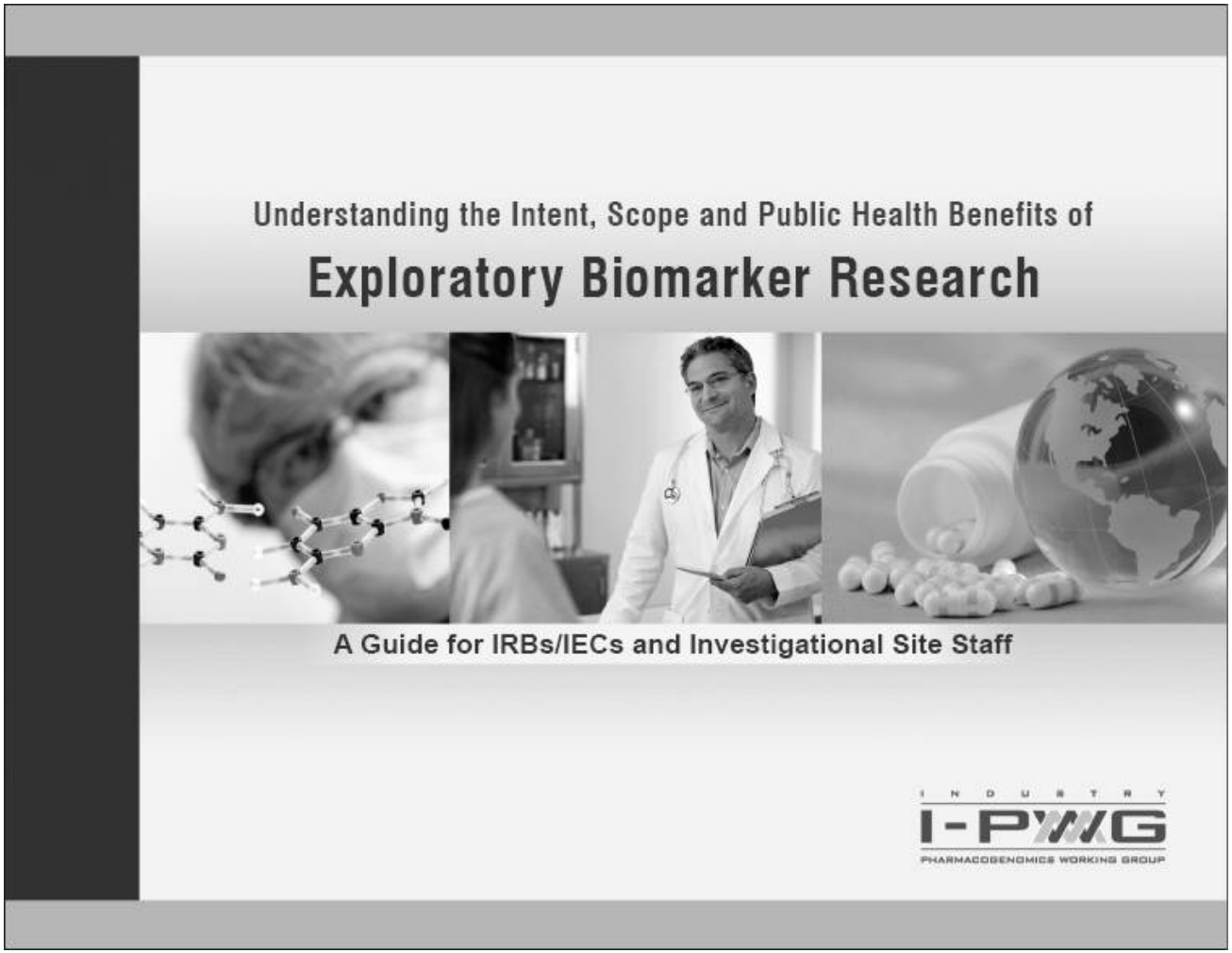
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

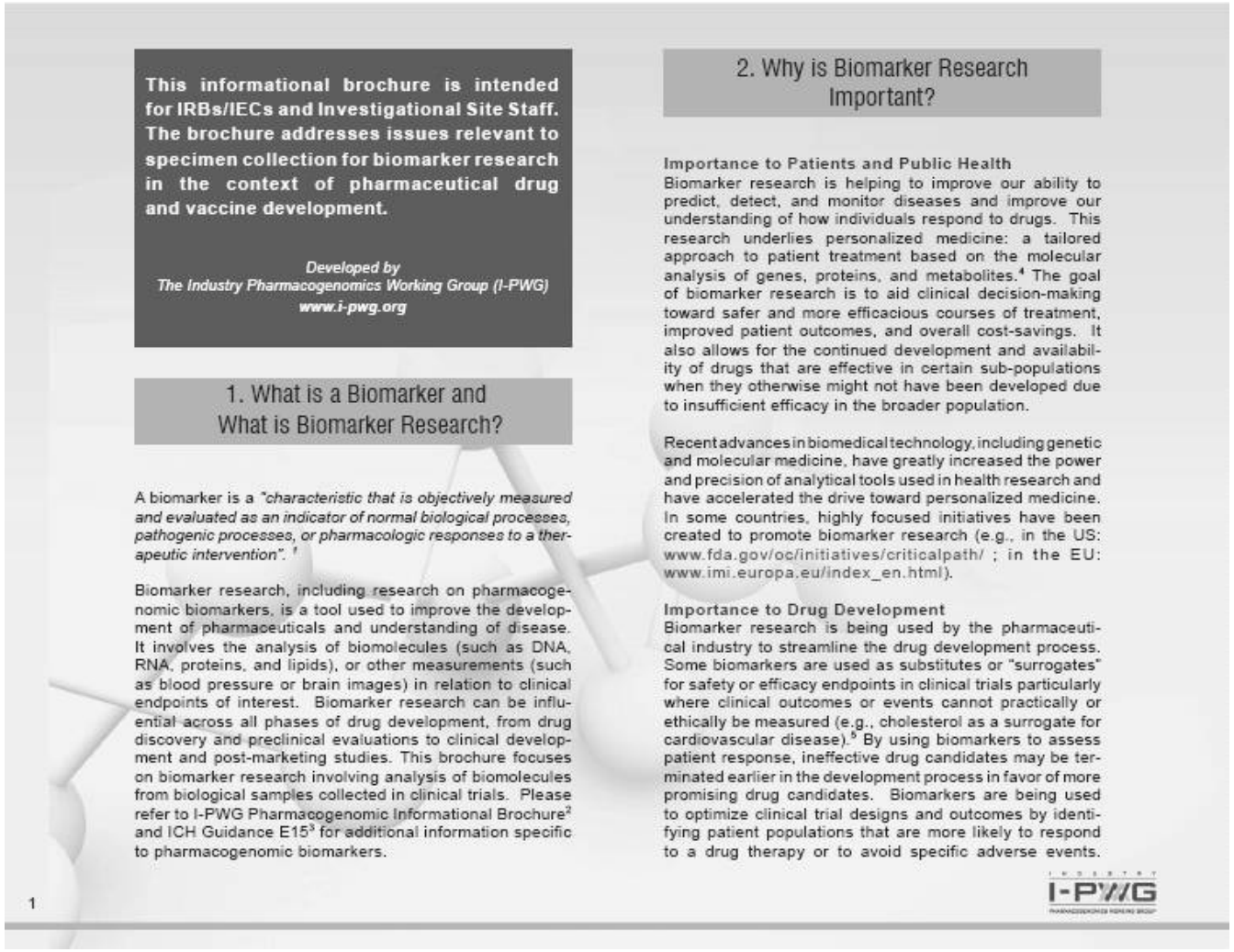
13. References

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?

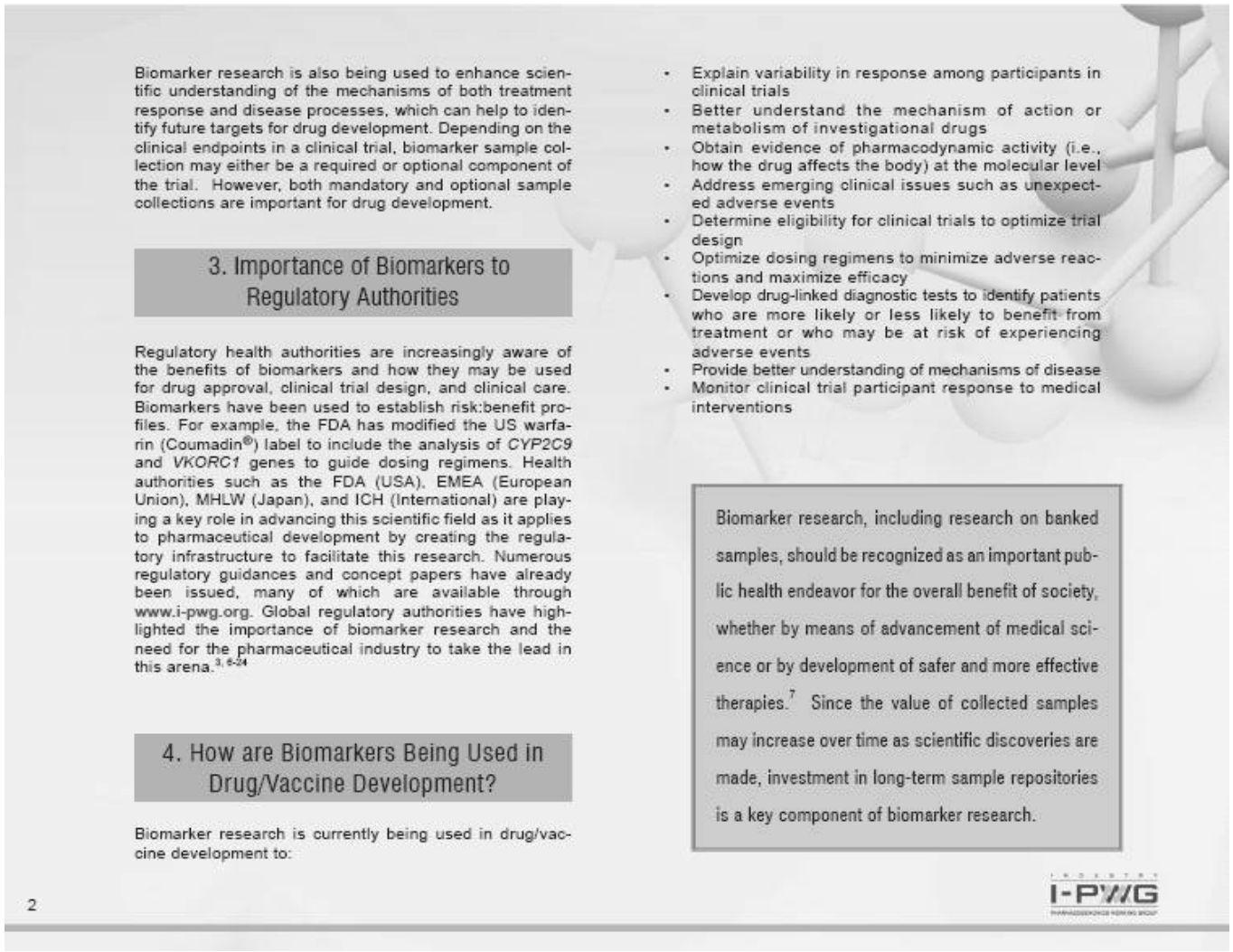
Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the 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.

I-PWG

1



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.

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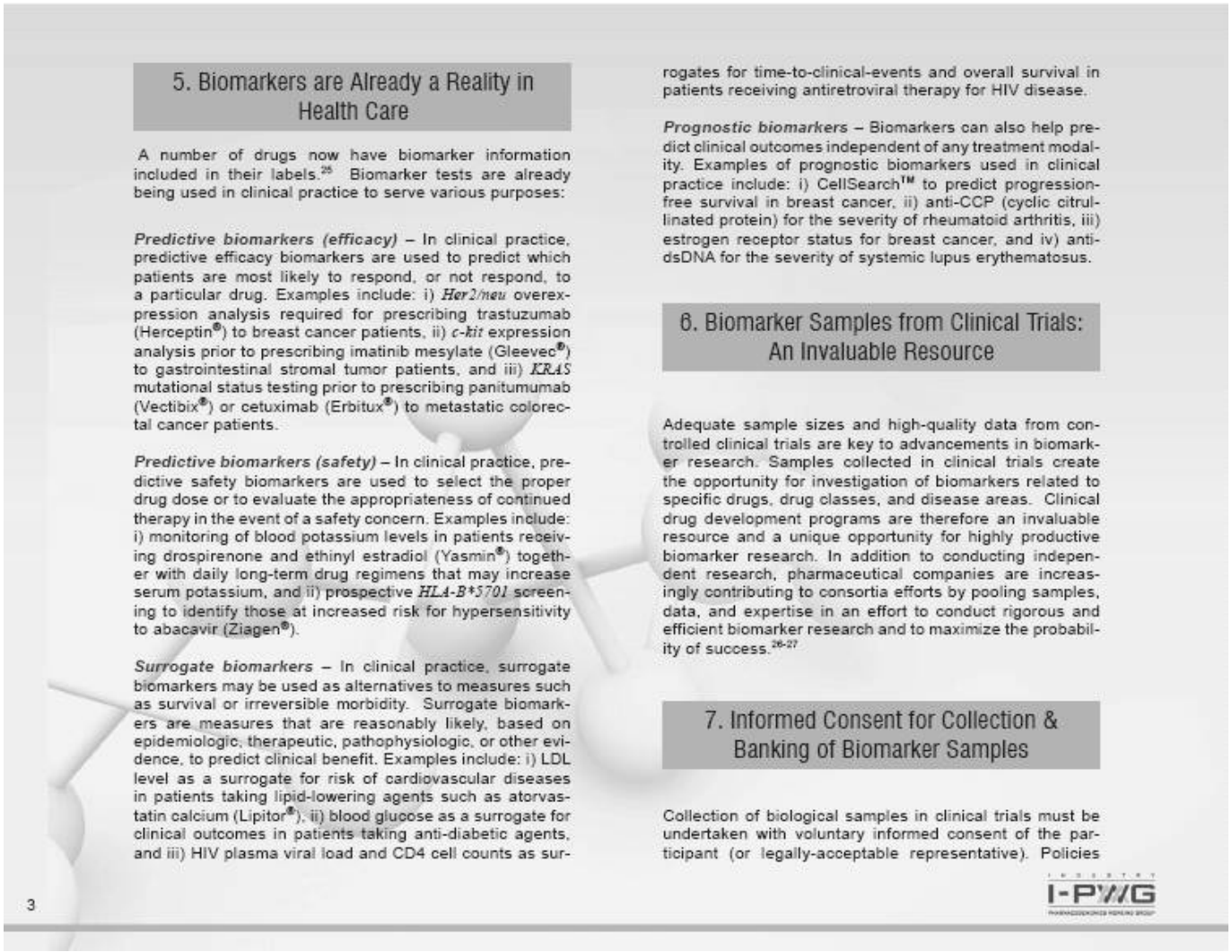

5. Biomarkers are Already a Reality in Health Care

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

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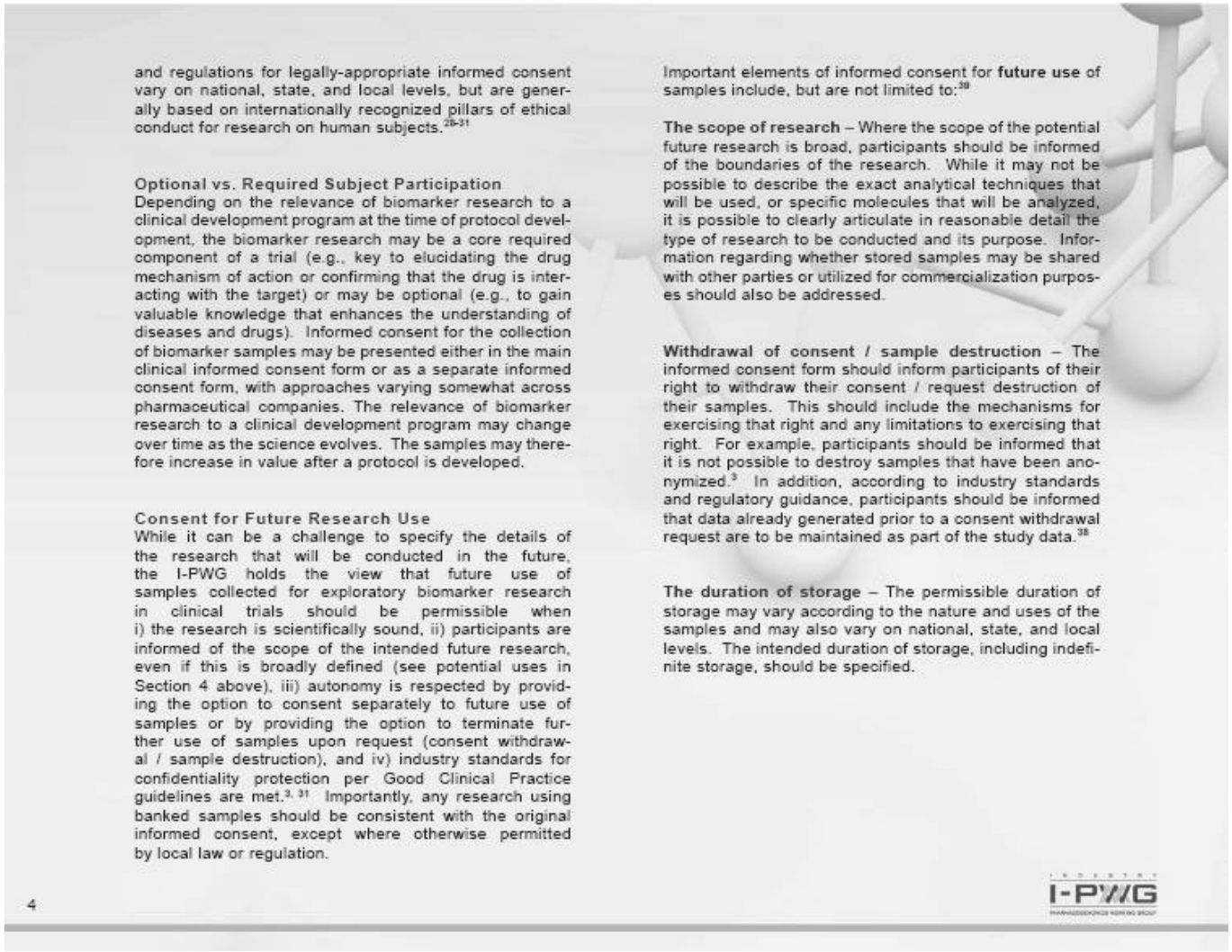

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

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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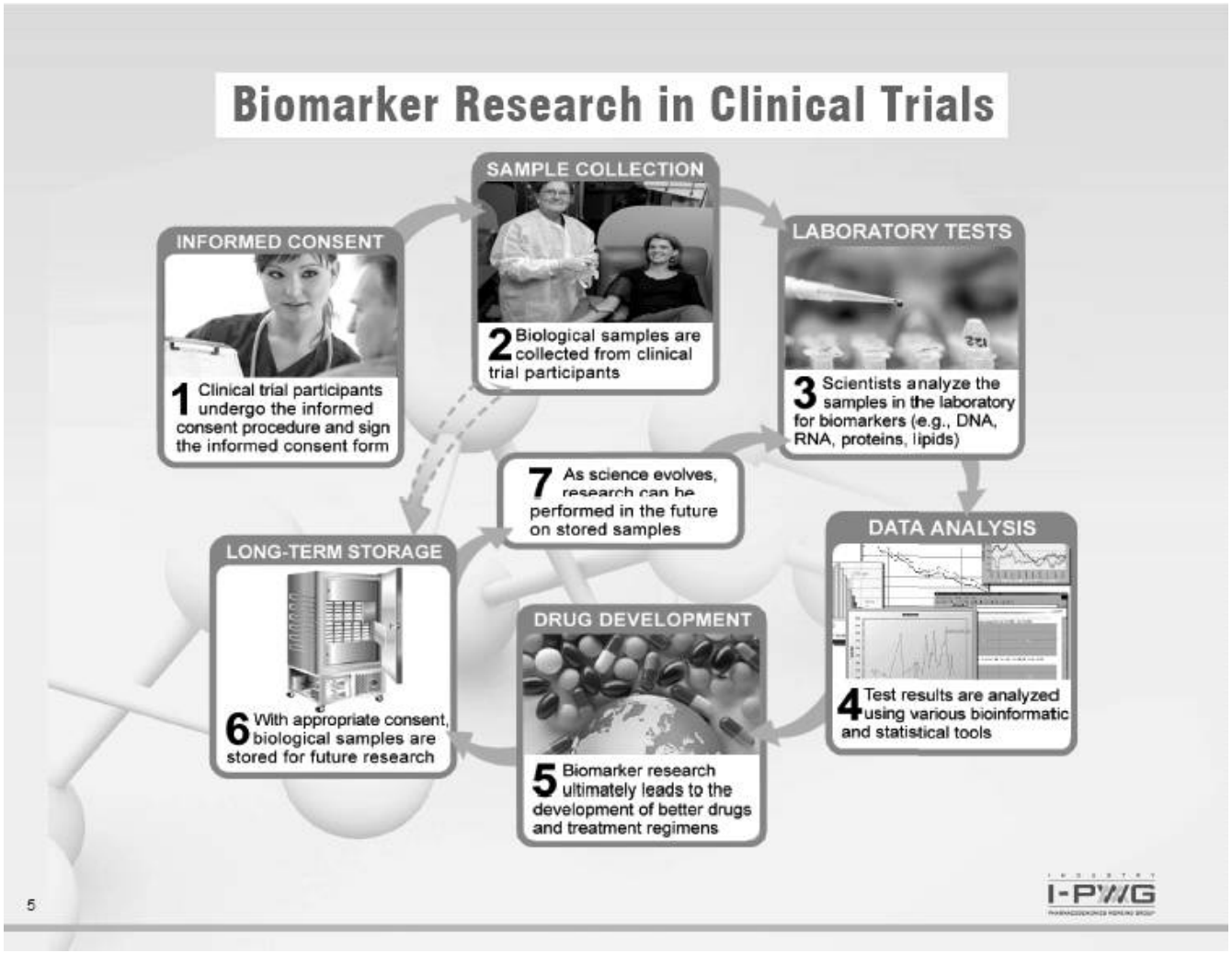
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the 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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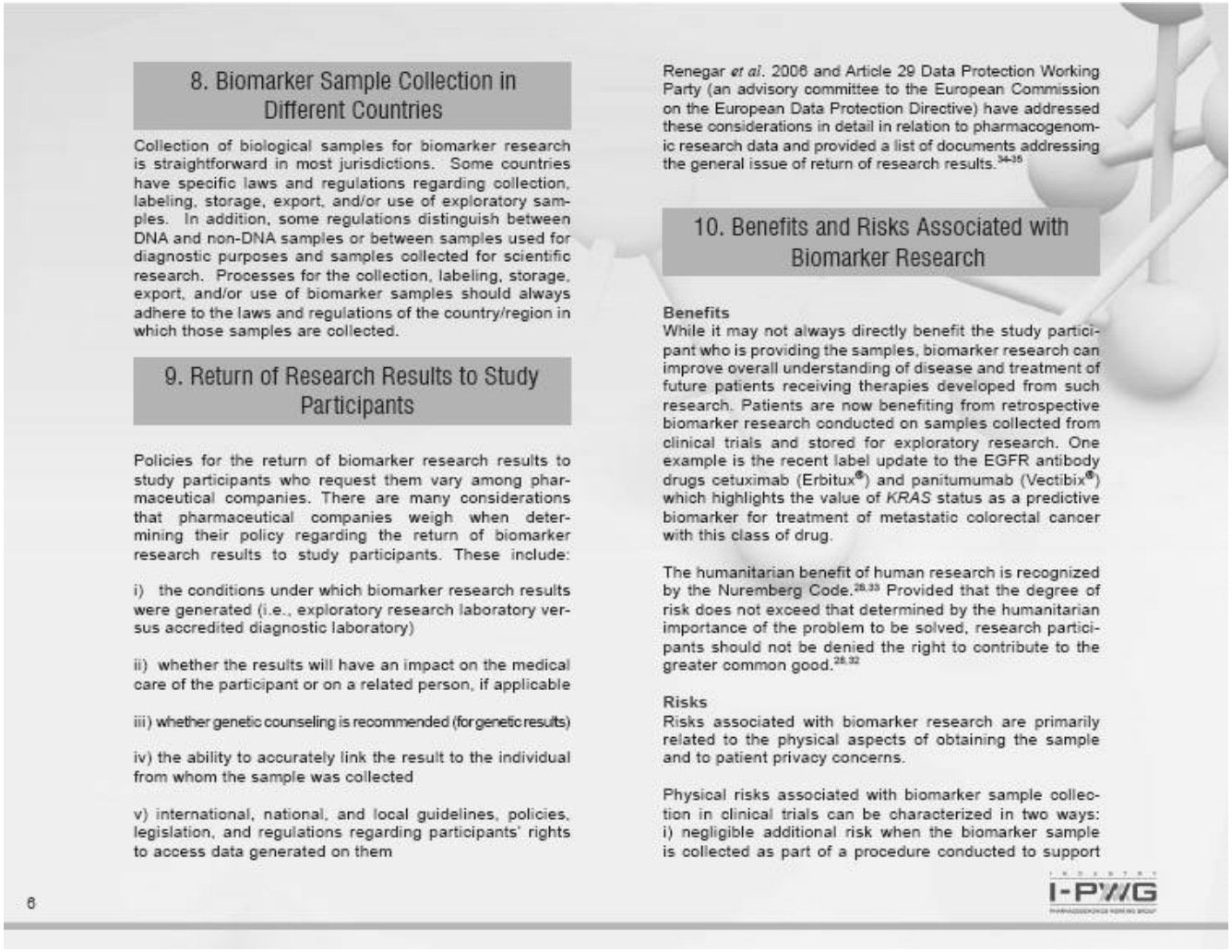

8. Biomarker Sample Collection in Different Countries

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.[26,33] 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.[26,32]

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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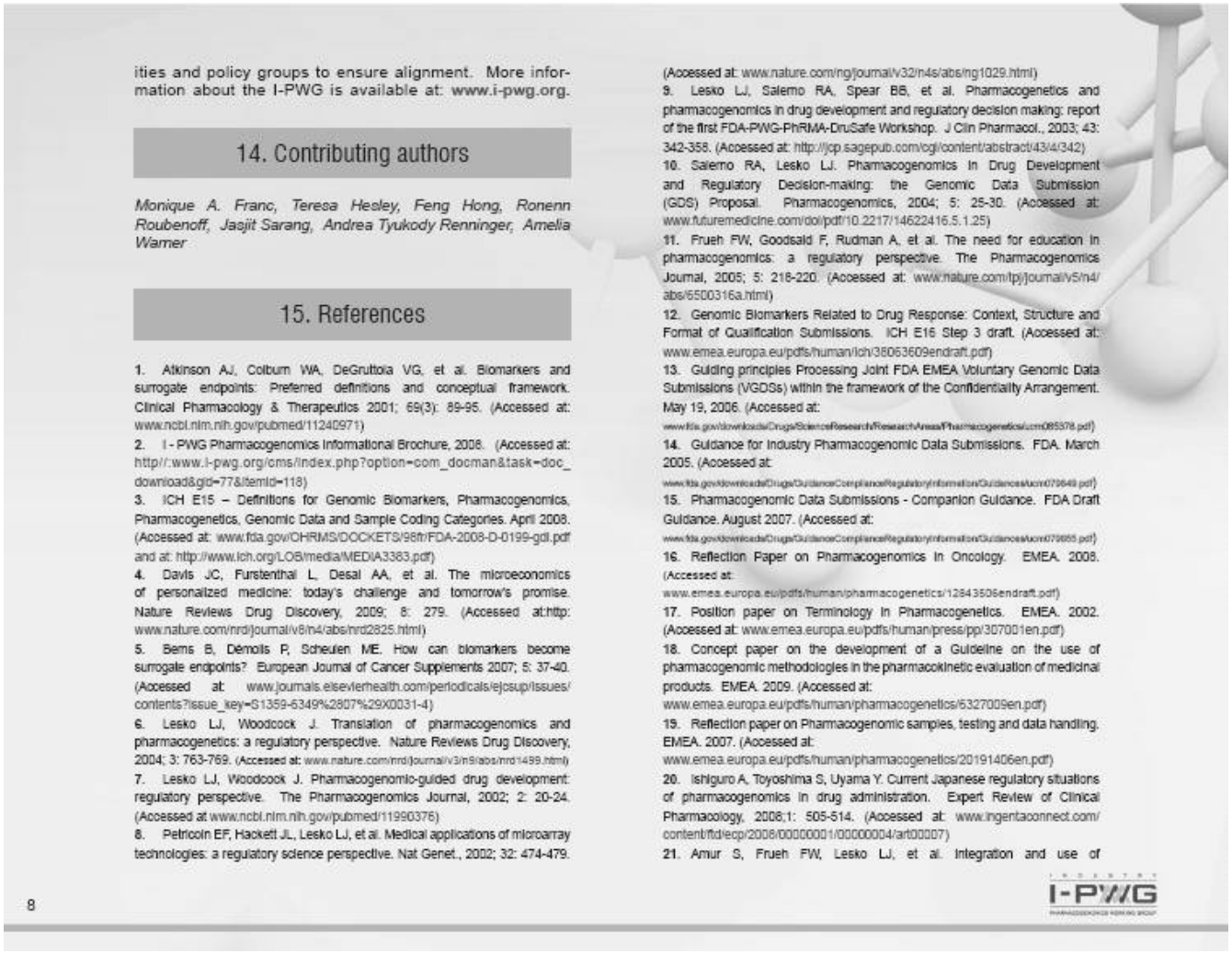

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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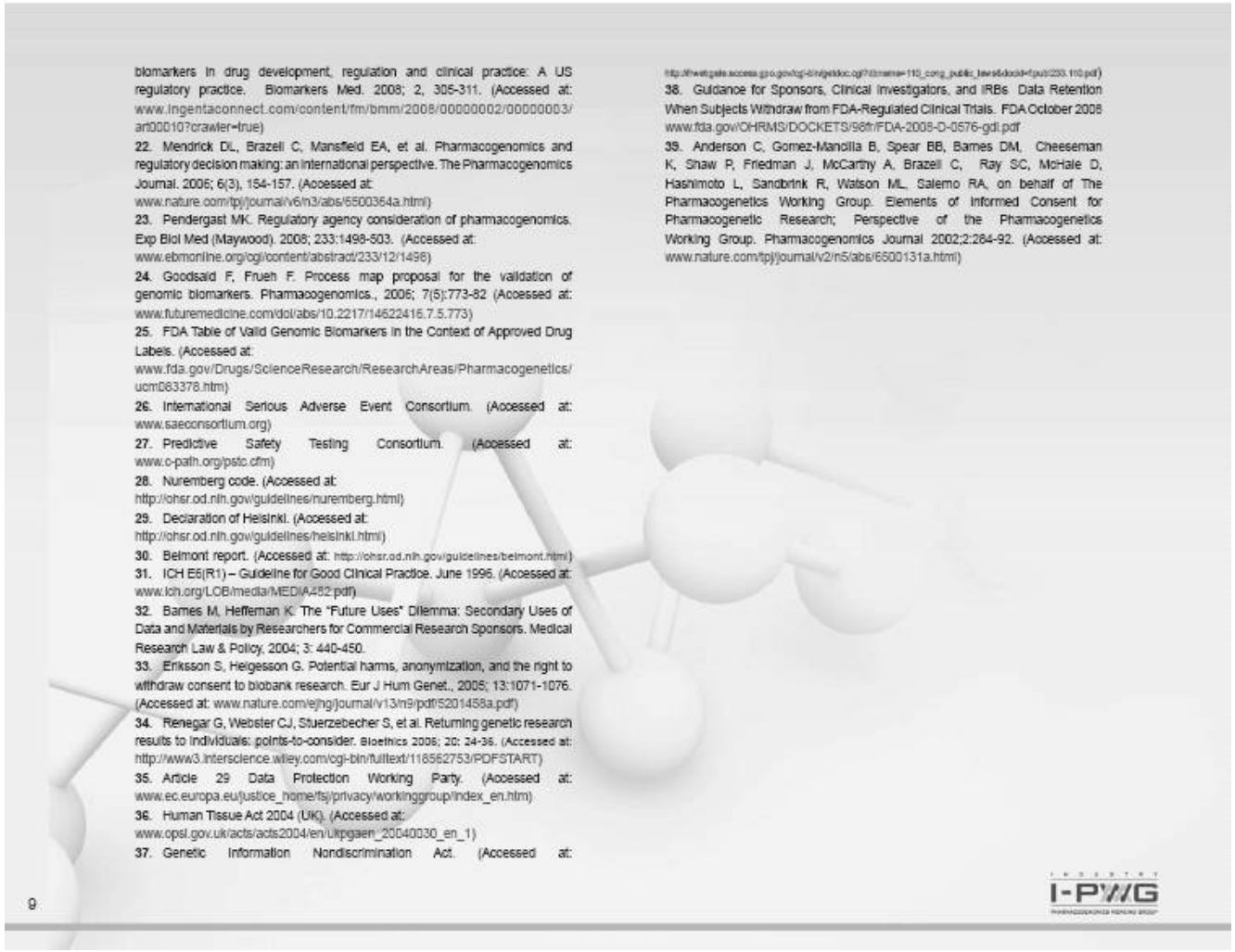

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12.4 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

RECIST 1.1* will be used in this study for assessment of tumor response. After initial disease progression, tumor response assessment will be per irRECIST for subjects on the pembrolizumab (MK-3475) arm (see Section 7.1.4.6).

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

12.5 ECOG Performance Status

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

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

12.6 Common Terminology Criteria for Adverse Events v4.0

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 List of Abbreviations

Abbreviation/Term	Definition
1L	First Line
5-FU	5-fluorouracil
AE	Adverse Event
ADA	Anti-Drug Antibodies
ADL	Activities of Daily Living
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
API	Asian/Pacific Islander
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
CEA	Carcinoembryonic Antigen
CBC	Complete Blood Count
CI	Confidence Interval
CIV	Central Imaging Vendor
CL	Clearance
Cmax	Maximum Concentration
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Carcinoma or Colorectal Cancer
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Study Facilitation Group
CTL	Cytotoxic T Cell
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
Ctrough	Minimum Concentration
DKA	Metabolic Acidosis
DMC	Data Monitoring Committee
dMMR	Mismatch Repair Deficient
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DPD	Dihydropyrimidine Dehydrogenase
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eDMC	external Data Monitoring Committee
EGFR	Epidermal Growth Factor Receptor
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EPO	Erythropoietin
ePRO	Electronic Subject Reported Outcomes
ER	Emergency Room
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
EU	European Union
FBR	Future Biomedical Research

Abbreviation/Term	Definition
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FT3	Free Total Triiodothyronine
FT4	Free Thyroxine
GCP	Good Clinical Practice
GI	Gastrointestinal
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDO	Indoleamine 2,3-Dioxygenase
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IFNγ	Interferon Gamma
INR	International Normalized Ratio
irRECIST	Immune-related RECIST
irRC	Immune-Related Response Criteria
IRB	Institutional Review Board
ITT	Intention-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
JSCCR	Japanese Society for Cancer of the Colon and Rectum
Kg	Kilogram
LAG-3	Lymphocyte-Activation Gene 3
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mcL	Microliters
Mg	Milligram
Mg/kg	Milligram per Kilogram
MHC	Major Histocompatibility Complex
mL	milliliter
mRNA	Messenger RNA
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI-H	Microsatellite Instability-High
MSS	Microsatellite-Stable
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival

Abbreviation/Term	Definition
OTC	Over-the-Counter
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-Free Survival
PD-1	Programmed Death 1
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death Ligand 2
PIN	Personal Identification Number
PK	Pharmacokinetic
PR	Partial Response
PRO	Subject Reported Outcomes
PT	Prothrombin Time
PTT	Partial Prothrombin Time
PS	Performance Status
QALY	Quality Adjusted Life Years
QoL	Quality-of-Life
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q9W	Every 9 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted Mean Survival Time
RNA	Ribonucleic Acid
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIM	Site Imaging Manual
SLD	Sum of Longest Diameters
SOC	Standard of Care
SOP	Standard Operating Procedures
sSAP	Supplemental Statistical Analysis Plan
T1DM	Type 1 Diabetes Mellitus
T3	Total Triiodothyronine
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
US	United States
V	Volume of Distribution
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

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 – 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	