For Protocol Amendment #12 to: NRG-GY018

NCI Protocol #: NRG-GY018
Local Protocol #: NRG-GY018

NCI Version Date: February 24, 2023

This amendment is being submitted in response to an RRA from Dr. Elad Sharon (sharone@mail.nih.gov):

Section	Comments
Title Pages	NCI Version Date is now February 24, 2023.
6.2	NCI has updated the dose modification guidelines for pembrolizumab.
6.2.3, 6.2.4	The tables in 6.2.3 and 6.2.4 were replaced with updated dose modification guidelines for pembrolizumab.
6.2.5	This section, neurological toxicities, was added and the remaining section was renumbered.

7.3	The CAEPR for pembrolizumab has been updated to Version 2.7, December 13, 2022:
	• Added New Risk:
	  • Rare but Serious: Endocrine disorders - Other (hypoparathyroidism); Nervous system disorders - Other (optic neuritis)
	• Decrease in Risk Attribution:
	  • Changed to Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution from Less Likely: CPK increased; Joint effusion; Pleuritic pain
	• Deleted:
	  • Less Likely: Avascular necrosis; Immune system disorders - Other (pseudoprogression/tumor inflammation); Infection; Musculoskeletal and connective tissue disorder - Other (tenosynovitis)
	  • Footnote #4 “Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.” is deleted.

ICD	Please see the ICD for additional changes.

In addition, the following changes were made:

Section	Comments
Title Page	• The date of closure to accrual was added. • CTSU Logistical language was updated.
Schema	"On February 6, 2023, all patient treatment assignments were unblinded and made available through Medidata Rave. Patients randomized to Arm 1 will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol. Patients on Arm 2 will continue all study related treatments and evaluation" was added.
5.	"On February 6, 2023, all patient treatment assignments were unblinded and made available through Medidata Rave. Patients randomized to Arm 1 will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol. Patients on Arm 2 will continue all study related treatments and evaluations" was added.
5.2	"Effective February 06, 2023, all patients have been unblinded. Patients randomized to Arm 1 will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol. Patients on Arm 2 will continue all study related treatments and evaluations" was added.
8.1	CTSU Logistical language was updated.
8.2	CTSU Logistical language was updated.
8.2	The Delegation of Tasks Log section was updated to reflect the unblinding of all patients as of February 6, 2023. A new DTL (without the Unblinded Study Personnel task) is available on the CTSU website and must be completed and signed by the site CI.
8.3/8.3.1	CTSU Logistical language was updated.
8.4	• CTSU Logistical language was updated. • Central Monitoring Section was added.
8.5, 8.5.1, 8.5.2	• References to Unblinded Study Personnel were removed. • OAOP has been replaced with AURORA.
8.5.3	Agent Accountability information was updated.
8.5.4	OAOP has been replaced with AURORA.
9.1.4	This section was updated.
9.1.5	This section was updated.
9.1.6	This section was updated.
9.2.2	This section was updated due to the unblinding of all patients as of February 6, 2023.

9.2.3	This section was updated.
9.2.4	• The drug order timeline/shipment chart was updated. • OAOP was replaced with AURORA. • References to Unblinded Study Personnel were removed. • Vial transfer information was updated. • Drug Return information was updated.
13.1	This section was removed as it was duplicative with information in Section 8.4. Remaining sections were renumbered.
Appendix VII	• In the Approximate scan collection per subject section, #2 was revised and #3 was deleted for better consistency with Section 4.2. • CTSU Logistical language for TRIAD was updated.
Appendix IX	• "On February 6, 2023, all patient treatment assignments were unblinded. Submission and maintenance of a Pharmacy Agreement for unblinded site personnel is no longer required. . ." was added. A new DTL (without the Unblinded Study Personnel task) is available on the CTSU website and must be completed and signed by the site CI. • "As of the unblinding of all patients on February 6, 2023, this Pharmacy Agreement no longer applies" was added to the top of the Agreement.
Appendix XIV	"Effective February 06, 2023, all patients were unblinded. Patients randomized to placebo (Arm 1) will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol" was added to the end of the appendix.

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NRG-GY018

***(ClinicalTrials.gov NCT # 03914612)* (09/24/2019)**

A PHASE III RANDOMIZED, PLACEBO-CONTROLLED STUDY OF PEMBROLIZUMAB (MK-3475, NSC #776864) IN ADDITION TO PACLITAXEL AND CARBOPLATIN FOR MEASURABLE STAGE III OR IVA, STAGE IVB OR RECURRENT ENDOMETRIAL CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; SWOG; and the Canadian Cancer Trials Group (CCTG).

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

Study Team (07/03/2019) (14-OCT-2020)	
Principal Investigator/Gyn Oncology	**Gyn Oncology Co-Chair**
Ramez N. Eskander, M.D.	**Amanda N. Fader, M.D.**
UC San Diego Moores Cancer Center	The Kelly Gynecologic Oncology Service
3855 Health Sciences Drive	600 N. Wolfe Street, Phipps 287
La Jolla, CA 92093-0987	Baltimore, MD 21287
858-822-6199/ FAX: 858-822-6319	410-955-8240/ FAX:
reskander@health.ucsd.edu	AFader1@jhmi.edu
Statistician	**CCTG Study Co-Chair**
Michael Sill, Ph.D.	**Stephen Welch, M.D.**
NRG Oncology Biostatistical Center-Buffalo	London Regional Cancer Program
Elm and Carlton Streets	790 Commissioners Road East
Buffalo, NY 10065	London, ON Canada N6A 4L6
716-845-5702/FAX: 716-845-8393	519-685-8640
sillm@nrgoncology.org	Stephen.welch@lhsc.on.ca
Patient Reported Outcomes Co-Chair	**Translational Scientist**
Lari Wenzel, Ph.D.	**Heather A Lankes, Ph.D., M.P.H**
UC Irvine Health	NRG Oncology
Chao Family Comprehensive Cancer Center	Four Penn Ctr, 1600 JFK Blvd., Ste 1020
100 Theory Street, Suite 110	Philadelphia, PA 19103
Irvine, CA 92697	lankesh@nrgoncology.org
lwenzel@uci.edu	

Research Nurse (14-OCT-2020)	**Data Manager**
Vania Hom	**Ashley Badders**
Memorial Sloan Kettering Cancer Ctr	NRG Oncology SDMC-Pittsburgh
1275 York Ave	201 N. Craig St., Suite 500
New York, NY 10065	Pittsburgh, PA 15213
646-888-4227	412-624-5532/FAX: 412-624-1082
homv@mskcc.org	baddersa@nrgoncology.org
Protocol Coordinator	
Meg Colahan, M.A.	
NRG Oncology	
Four Penn Ctr, 1600 JFK Blvd., Ste 1020	
Philadelphia, PA 19103	
267-295-9476/FAX: 215-854-0716	
colahanm@nrgoncology.org	

The following NCTN Group Study Champion has been added to this trial:
CCTG: **Stephen Welsh, M.D.**, London Regional Cancer Program, Stephen.welch@lhsc.on.ca

NRG Oncology Contact Information (07/03/2019) (21-MAY-2021)	
Data Management For questions concerning data submission	Ashley Badders NRG Oncology Statistics and Data Management Center-Pittsburgh 201 N. Craig St., Suite 500 Pittsburgh, PA 15213 412-624-5532/FAX 412-624-1082 baddersa@nrgoncology.org
Protocol Development For questions concerning protocol and informed consent versions and amendments	Protocol Coordinator Meg Colahan, M.A. NRG Oncology-Philadelphia East Four Penn Center, 1600 JFK Blvd., Ste 1020 Philadelphia, PA 19103 267-295-9476 colahanm@nrgoncology.org
Regulatory	NRG-GY-Regulatory@nrgoncology.org
Biospecimen Bank	NRG BB-Columbus Biopathology Center, Nationwide Children's Hospital 700 Children's Dr, WA1340 Columbus, OH 43205 Phone: 866-464-2262/FAX: 614-722-2897 Email: bpcbank@nationwidechildrens.org

Gynecologic Oncology Committee Chair	Carol Aghajanian, M.D. Memorial Sloan Kettering Cancer Center Department of Medicine 1275 York Avenue New York, NY 10065 (646) 888-4217 aghajanc@mskcc.org

Protocol Agents (09/24/2019)

Agent	Supply	NSC #	IND #	IND Sponsor
Pembrolizumab (MK-3475)	CTEP	776864		DCTD, NCI
Carboplatin	Commercial	241240	N/A	N/A
Paclitaxel	Commercial	673089	N/A	N/A

Participating Sites

☒ U.S.
☒ Canada
☒ Approved International Member Sites

Document History

	Version Date
Amendment 12	**February 24, 2023**
Closed to Accrual	December 06, 2022
Amendment 11	September 30, 2022
Amendment 10	May 19, 2022
Amendment 9	March 9, 2022
Amendment 8	October 6, 2021
Amendment 7	May 21, 2021
Amendment 6	December 08, 2020
Amendment 5	October 14, 2020
Amendment 4	February 27, 2020
Amendment 3	February 07, 2020
Amendment 2	09/24/2019
Amendment 1	07/03/2019
Initial	06/14/2019

NRG ONCOLOGY

NRG-GY018

A PHASE III RANDOMIZED, PLACEBO-CONTROLLED STUDY OF PEMBROLIZUMAB (MK-3475, NSC #776864) IN ADDITION TO PACLITAXEL AND CARBOPLATIN FOR MEASURABLE STAGE III OR IVA, STAGE IVB OR RECURRENT ENDOMETRIAL CANCER

CONTACT INFORMATION (14-OCT-2020) (21-MAY-2021) (09-MAR-2022) (24-FEB-2023)

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires logging in with a CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP0-IAM accounts and by July 1, 2023 for all users). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
For imaging submission questions, contact IROCPHILA-DI@acr.org.

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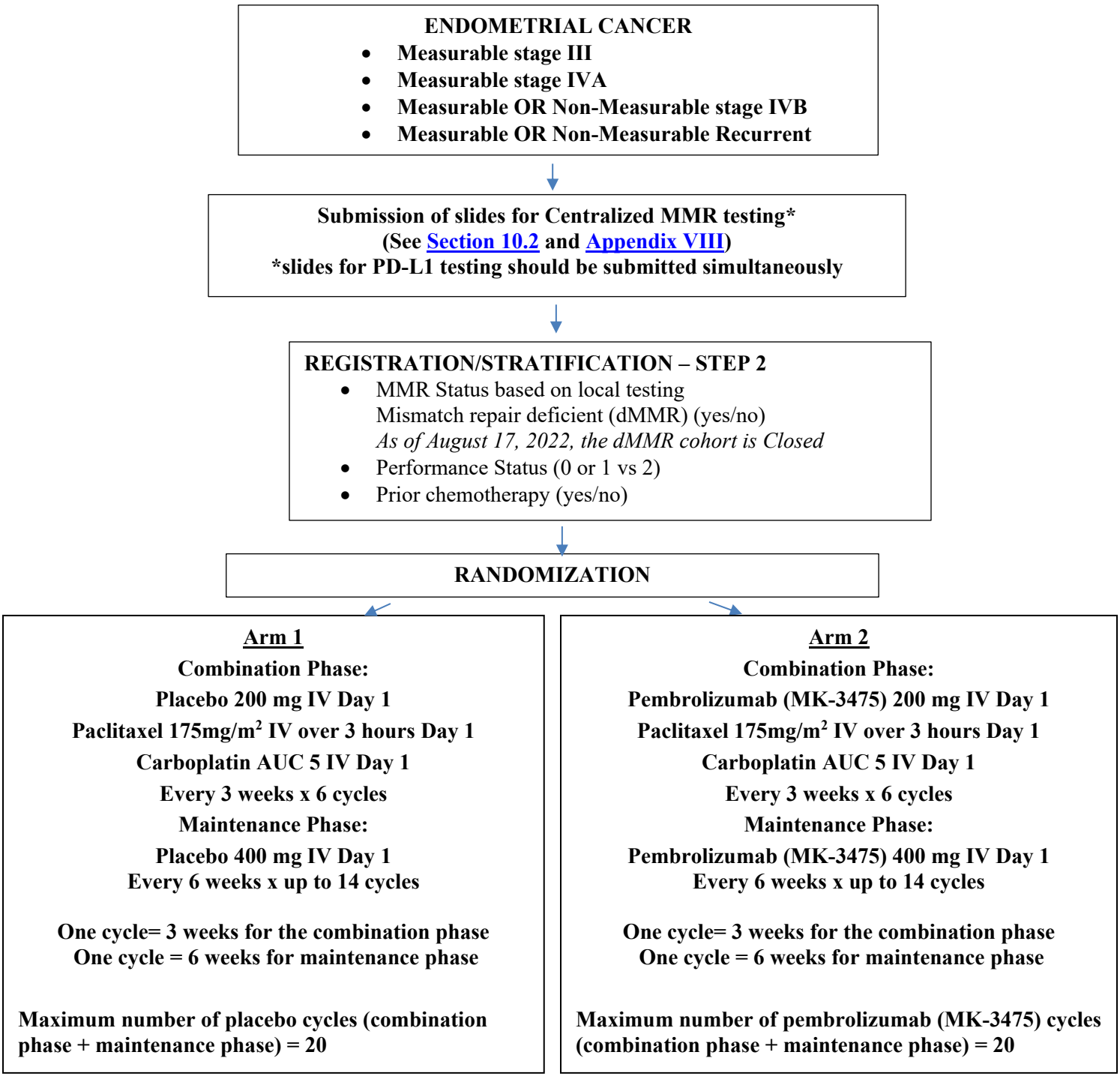
NRG-GY018 SCHEMA (09/24/2019) (07-FEB-2020) (14-OCT-2020) (21-MAY-2021) (09-MAR-2022) (30-SEP-2022) (24-FEB-2023)



On February 6, 2023, all patient treatment assignments were unblinded and made available through Medidata Rave. Patients randomized to Arm 1 will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol. Patients on Arm 2 will continue all study related treatments and evaluations.

Abbreviations: **(07/03/2019)**

dMMR	Mismatch repair deficient
pMMR	Mismatch repair proficient
IHC	Immunohistochemistry
MMR	Mismatch repair proteins (MLH1, MSH2, MSH6, PMS2)
MSI	Microsatellite instability
MSI-H	Microsatellite instability – high
MSS	Microsatellite stable
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1

1. OBJECTIVES

1.1 Primary Objective

1.1.1 To evaluate the efficacy of pembrolizumab (MK-3475) in combination with paclitaxel and carboplatin in patients with advanced stage (measurable stage III or IVA), stage IVB and recurrent endometrial cancer. Efficacy will be determined via investigator assessed progression free survival (PFS) as assessed by RECIST 1.1 in two distinct populations referred to as proficient and deficient mismatch repair (pMMR and dMMR). **(07/03/2019)**

1.2 Secondary Objectives (07/03/2019)

1.2.1 To determine the nature, frequency and degree of toxicity as assessed by CTCAE for each treatment arm.

1.2.2 To evaluate BICR assessed or investigator assessed objective response rate (ORR) as assessed by RECIST 1.1 by treatment arm and by MMR IHC status in patients who enter the study with measurable disease. **(09-MAR-2022)**

1.2.3 To evaluate BICR assessed or investigator assessed duration of response (DOR) by treatment arm and by MMR IHC status in patients who enter the study with measurable disease. **(09-MAR-2022)**

1.2.4 To evaluate the effect of pembrolizumab (MK-3475) on OS in patients with pMMR or dMMR.

1.2.5 To determine whether the addition of pembrolizumab (MK-3475) to standard combination chemotherapy is associated with improved patient reported physical function as measured with the PROMIS-physical function scale (short form), quality of life as measured with the FACT-En TOI and worsened fatigue as measured with the PROMIS-Fatigue scale (short form) in the pMMR patients.

1.2.6 To determine concordance between institutional MMR IHC testing and centralized MMR IHC.

1.3 Exploratory objectives

1.3.1 To explore the correlation between patient-reported physical function as measured with the PROMIS-physical function scale (short form) and quality of life as measure with the FACT-En TOI.

1.3.2 To explore whether the addition of pembrolizumab (MK-3475) to standard combination chemotherapy is associated with self-reported neurotoxicity as measured with the FACT/GOG-Ntx subscale (short) and the extent to which patients differ on their self-reported bother from side effects of cancer therapy in the pMMR patients.

1.3.3 To evaluate the efficacy of pembrolizumab (MK-3475) in combination with paclitaxel and carboplatin in patients with advanced stage (measurable stage III or IVA), stage IVB and recurrent endometrial cancer by PD-L1 IHC (positive vs negative). Efficacy will be determined via investigator assessed progression free survival (PFS) and overall survival (OS) in two distinct populations referred to as proficient and deficient mismatch repair (pMMR and dMMR).

1.3.4 To assess the association between PD-L1 IHC (positive vs negative) and mismatch repair status (pMMR and dMMR).

2. BACKGROUND (07/03/2019) (14-OCT-2020)

Endometrial cancer (EC) continues to be the most common gynecologic malignancy in the United States and is the only cancer of the female genital tract with a rising incidence and mortality (Evans, 2011). In 2017 there were an estimated 61,380 new cases and 10,920 deaths (Siegel, 2017). Despite the excellent prognosis in patients with early stage disease, those with advanced stage, metastatic or recurrent EC have limited therapeutic options with long-term survival approaching 15%, representing an **area of unmet clinical need**. Since the completion of Gynecologic Oncology Group (GOG) protocol 177, which explored the triplet regimen of paclitaxel, doxorubicin, and cisplatin (TAP) in patients with advanced stage and recurrent EC, there have been limited therapeutic advancements (Fleming, 2004). GOG 209 was a phase 3 clinical trial comparing the combination regimen of paclitaxel and carboplatin to TAP. This study enrolled over 1300 subjects and demonstrated less toxicity and a non-inferior PFS and OS with the doublet regimen, rendering paclitaxel and carboplatin the backbone for future clinical trials (Miller, 2012). Second line chemotherapy options for endometrial cancer are notably less effective, with megestrol acetate being the only FDA approved agent in this setting. A phase III randomized trial of second line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer did not meet its primary objective of improving OS in the ixabepilone arm compared to the control chemotherapy arm (McMeekin, 2015). OS, PFS and ORR were similar in both arms, with control chemotherapy showing median OS of 12.3 months, median PFS of 4 months and ORR of 15.7% (all partial responses).

Immunotherapy has emerged as a therapeutic strategy in patients with advanced stage or recurrent EC (Vanderstraeten, 2014, Coosemans, 2014). The clinical relevance of immunotherapy in the treatment of solid malignancies is well established, with checkpoint inhibitors approved for the treatment of several solid malignancies: melanoma, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, and non small cell lung cancer. Most recently, the anti-PD-1 antibody pembrolizumab (MK-3475, Keytruda®) was granted FDA approval as monotherapy in patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) solid tumors, whose disease has progressed following prior therapy, and who have no satisfactory alternative treatment options (including endometrial carcinoma). This approval was partially based on the promising results reported with single agent checkpoint inhibition in patients with heavily pretreated, dMMR or MSI-H endometrial cancer. In an effort to improve response rates, and oncologic outcomes in this patient population, we propose a randomized, placebo-controlled phase III study examining paclitaxel and carboplatin combination chemotherapy with the checkpoint inhibitor, pembrolizumab (MK-3475) or placebo in patients with advanced stage or recurrent endometrial cancer.

Identifying a more effective treatment strategy in this vulnerable population that translates into an improvement in outcomes, would represent a significant oncologic achievement. Furthermore, understanding the role of checkpoint inhibition in endometrial cancer, for both the mismatch repair deficient and microsatellite stable populations, may inform future studies and allow for the inclusion of immunotherapeutic treatment paradigms in clinical trial designs targeting earlier stage disease. Ultimately, the goal would be to improve the quality of life and outcomes for women affected by these aggressive cancers.
Disease progression in patients with recurrent endometrial cancer can present clinically,

requiring history and physical examination to guide identification and inform treatment/patient counseling. In context of the above, it is recommended that patients be seen and examined with appropriate interval history and physical examination as part of routine care and on clinical trial. Assessment intervals of 6-weeks will allow for patient evaluation and is a reasonable examination schedule. Thus, because it is appropriate to see patients every 6 weeks for health monitoring, it is reasonable to incorporate every 6-week placebo/pembrolizumab administration schedule into the study protocol as outlined in section 4.2.

2.1 Immunotherapy in endometrial cancer

Immunohistochemical studies on EC specimens have detailed PD-1 and PD-L1 expression levels surpassing those seen in ovarian and cervical carcinoma (Vanderstraeten, 2014, Herzog, 2015)(Table 1) (Brahmer, 2012).

Table 1: PD-1 and PD-L1 expression levels in uterine cancer (450 specimens) (Herzog, 2015)

Histology	PD-1	PD-L1
	% Expression based on IHC staining*	
Endometrioid	77.9	39.7
Serous Carcinoma	68.2	10.2
Carcinosarcoma	80.0	22.2
Clear Cell Carcinoma	69.2	23.1

* IHC antibody = Spring Bioscience (Rabbit anti-Human IgG)

A compelling argument for the use of immune checkpoint inhibitors in EC was put forth by a phase 2 trial of pembrolizumab (MK-3475), in patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H), progressive metastatic carcinoma (Le, 2015). This trial was designed to test the hypothesis that dMMR or MSI-H, tumors are more responsive to PD-1 blockade than microsatellite stable (MSS) tumors, due to the high somatic mutational load, resulting in neo-antigen formation and a more prominent lymphocytic infiltrate. As predicted, the two cohorts with dMMR or MSI-H cancers (one with colorectal cancer patients and the other with non-colorectal cancer patients, including 2 patients with recurrent, previously treated endometrial cancer) had significantly higher objective response rates by immune-related response criteria and by Response Evaluation Criteria in Solid Tumors (RECIST). The MSI-H cohorts also experienced a significantly better immune-related PFS and disease control rate at 20 weeks by RECIST. Building upon this, A.N. Fader et al. presented an expanded cohort of dMMR, recurrent or persistent, endometrial cancer patients treated with single agent pembrolizumab (MK-3475) (An, 2016). All 10 patients received at least 1 prior line of systemic chemotherapy, and up to 4 previous regimens. The authors reported an overall response rate of 70% (95% CI 21%–86%, n = 7), with 2 complete responses (CR) and 5 partial responses (PR). The disease control rate, or "clinical benefit" rate (CR + PR + stable disease), was 80% (n = 8). The 12-month overall survival (OS) rate was 89%, and the median OS was not yet reached. Importantly, MSI

status was determined using standard of care MMR IHC testing for MLH1, MSH2, MSH6, and PMS2. Patients lacking expression of DNA mismatch repair proteins were classified as dMMR or MSI-H, consistent with prior studies reporting concordance rates great than 90% between MMR IHC and MSI PCR.

Most recently, following review of pooled data from five uncontrolled, open-label, multi-cohort, multi-center, single arm trials, single agent pembrolizumab (MK-3474) was approved for the treatment of dMMR or MSI-H solid tumors that progressed following prior therapy, with no alternative treatment options. This disease site agnostic approval, issued by the FDA on 5-23-17, was the first of its kind, reflecting the clinical relevance of checkpoint inhibition in patients with limited therapeutic options. Across all 5 trials, the efficacy analysis showed an ORR of 39.6% (95% CI 31.7-47.9) with a complete response rate of 7.4% and a partial response rate of 32.2%. At the time of data cutoff, median duration of response had not yet been reached (range 1.6+ to 22.7+ months), with 78% of responding patients having responses of six months or longer. Of the 149 subjects in the pooled analysis, 14 had recurrent endometrial cancer, with a reported ORR of 36% (DOR range 4.2+, 17.3+), surpassing historical controls in this pretreated patient population.

Goodfellow et al. additionally confirmed MSI-H status in 28.4% (296 of 1043 EC specimens) of EC tumors examined as part of NRG/GOG-0210 (Goodfellow, 2015). Expanding on this assessment McMeekin et al. examined the clinicopathologic significance of MMR defects in a cohort of endometrioid endometrial cancers (NRG/GOG0210). Within this population, MMR defects were identified in 71 (42%) of 168 subjects with stage 3 or 4 disease. The frequency of MMR deficiency in the recurrent population was confirmed in an unpublished analysis of patients treated on GOG 86P, with nearly 40% of subjects with recurrent grade 2 or 3 endometrioid adenocarcinoma having absent PMS2 or MSH6 expression (data courtesy of Dr. Aghajanian).

Howitt et al examined the hypothesis that microsatellite unstable endometrial cancers would exhibit more tumor specific neo-antigens, resulting in increased tumor infiltrating lymphocytes and a compensatory up-regulation of immune checkpoints (Howitt, 2015). Microsatellite unstable tumors exhibited higher numbers of CD3+ and CD8+ tumor infiltrating lymphocytes. Furthermore, PD-1 was overexpressed in tumor infiltrating lymphocytes, and peri-tumoral lymphocytes of microsatellite unstable tumors. This combination of increased mutational load, tumor infiltrating lymphocytes, and high PD-1/PD-L1 expression makes endometrial cancer an ideal target for immunotherapeutic interventions.

These studies provide clinical evidence that immune checkpoint inhibitors may be effective in the treatment of endometrial cancer, and trials exploring this novel therapy in the front-line setting are both feasible and urgently needed.

2.2 Combining cytotoxic chemotherapy with immune checkpoint inhibitors: safety and efficacy

In order to improve on the number of patients responding to checkpoint inhibitors,

investigators are assessing combination regimens involving cytotoxic chemotherapy and PD-1/PD-L1 inhibition. Although no randomized controlled trials exist comparing single agent checkpoint inhibition to combination regimens with cytotoxic agents, preclinical data may support such an approach (Postow, 2015).

Several preclinical studies have indicated that cytotoxic chemotherapy may result in robust immune stimulation (Zitvogel, 2011). Platinum agents, including oxaliplatin, have been shown to result in immunogenic cell death (ICD), producing a favorable milieu for immune activations within tumor tissues (Ingeborg, 2016). Furthermore, taxanes, including docetaxel and paclitaxel, are known to modulate the anti-tumor immune response. As an example, concurrent paclitaxel therapy was shown to significantly enhance radiation-induced ICD in breast cancer cell lines (Golden, 2014). The anti-tumor effects of cytotoxic chemotherapy may additionally be immunologic, with a reduction in regulatory T-cell activity and an enhanced presentation of tumor cell specific antigens (Zitvogel, 2011, Galluzzi, 2015, Apetoh, 2015). Cytotoxic agents also appear to directly influence immune checkpoint expression. The in vitro treatment of dendritic cells (DCs) with platinum-based compounds strongly enhanced their potential to activate T-cells, via the downregulation of PD-L2 in DCs (Lesterhuis, 2011). This effect was the result of STAT6 inactivation, the transcriptional regulator of PD-L2, also occurring on tumor tissue, resulting in enhanced T cell recognition. Additionally, chemotherapy has been shown to induce PD-L1 expression on cancer cells (Peng, 2015). Thus, combining chemotherapy and immunotherapy may lead to enhanced anti-tumor effects.

Additional data supporting the investigation of a combinatorial approach comes from the phase I, CheckMate 012, multi cohort study reported by Rizvi et al (Rizvi, 2016). This study was conducted to explore the safety and efficacy of the anti-PD-1 immune checkpoint inhibitor, nivolumab, in combination with current standard therapies in first-line advanced non-small cell lung cancer (NSCLC). A total of 56 patients received nivolumab plus platinum-based doublet chemotherapy concurrently every 3 weeks for four cycles followed by nivolumab alone until disease progression or unacceptable toxicity. Regimens included nivolumab 10 mg/kg plus gemcitabine-cisplatin (squamous) or pemetrexed-cisplatin (non-squamous) or nivolumab 5 or 10 mg/kg plus paclitaxel-carboplatin (all histologies). The primary objective was to assess safety and tolerability. Secondary objectives included objective response rate and 24-week progression-free survival rate. Thirty of the 56 patients (54%) enrolled on study were female, and 38% received prior radiation therapy.

Importantly, no dose-limiting toxicities occurred during the first 6 weeks of treatment, and the most common toxicities reported for the combination were those anticipated with platinum doublet therapy alone. Furthermore, fewer than 10% of patients experienced treatment-related grade 3 or 4 leukopenia and anemia. Overall, 21% of patients discontinued therapy as a result of treatment-related AEs, although nearly all (10 of 12 patients (83%)) discontinued during the nivolumab monotherapy maintenance period. In the Nivolumab 10 mg/kg plus paclitaxel-carboplatin arm, the discontinuation rate was 13% (2 of 15 patients). Grade 3 or 4 treatment related AEs led to discontinuation in 14% of patients, most commonly as a result of pneumonitis and acute renal failure (5% [n=2] each). All discontinuations as a result of treatment related pneumonitis occurred during nivolumab monotherapy. The

paclitaxel + carboplatin + nivolumab regimen was associated with a favorable toxicity profile, and median OS was not reached during follow up (range 8.8 to 30.1+ months) (Rizvi, 2016).

Furthermore, the results of the phase 2 cohort of the open-label Keynote-021 study were recently published (Langer, 2016). Researchers enrolled a total of 123 patients with stage 3B/4 chemotherapy-naïve, nonsquamous, non-small cell lung cancer, to receive 4 cycles of carboplatin and pemetrexed (500mg/m^2 every 3 weeks), with or without 24 months of treatment with pembrolizumab (MK-3475) (200 mg every 3 weeks). After a median follow up of 10.6 months, patients receiving pembrolizumab (MK-3475) + chemotherapy exhibited a significantly greater objective response rate (55% vs. 29%, p = 0.0016) and an improved PFS (13 vs. 8.9 months; HR 0.53; 95% CI 0.31-0.91). Importantly, the entire study cohort was 61% female, with 38 of 60 patients (63%) in the pembrolizumab (MK-3475) plus chemotherapy cohort being women.

With respect to safety, the incidence of grade 3 or worse treatment-related adverse events was similar between groups (39% pembrolizumab (MK-3475) + chemotherapy vs. 26% chemotherapy alone), in the context of a 1.6-times longer exposure to treatment in the pembrolizumab (MK-3475) containing arm. The most common treatment related adverse events of any grade were fatigue (64% pembrolizumab (MK-3475) + chemotherapy vs 40% chemotherapy alone), nausea (58% vs. 44%), and anemia (32% vs. 53%). The most common grade 3 or worse treatment-related adverse events in the pembrolizumab (MK-3475) plus chemotherapy group were anemia (12%), neutropenia (3%), and acute kidney injury (3%) (Langer, 2016). In the chemotherapy alone group, the most common grade 3 or worse events were anemia (15%), neutropenia (3%), pancytopenia (3%), and thrombocytopenia (3%) (Langer, 2016). Six (10%) of 59 patients in the pembrolizumab (MK-3475) plus chemotherapy group and eight (13%) of 62 treated patients in the chemotherapy alone arm discontinued study treatment because of treatment related events. There was only one treatment related death in the pembrolizumab (MK-3475) arm of the study (1%, sepsis), compared to two in the chemotherapy alone group (3%, sepsis and pancytopenia). The most common immune-mediated adverse events of any grade in the pembrolizumab (MK-3475) plus chemotherapy group were hypothyroidism (15%), hyperthyroidism (8%), and pneumonitis (5%). Perhaps most strikingly, the incidence of potentially immune mediated adverse events in the pembrolizumab (MK-3475) plus chemotherapy group of the as-treated population (22%), was similar to that seen with pembrolizumab (MK-3475) monotherapy in KEYNOTE-010 (20% in the 2 mg/kg cohort; 19% in the 10 mg/kg cohort).

In Keynote 189 (Gandhi, 2018), a double-blind, randomized (2:1) phase 3 trial, 616 patients with NSCLC were randomized to receive platinum-chemotherapy and pemetrexed with pembrolizumab (MK-3475) or placebo and up 2 years of pemetrexed maintenance with pembrolizumab (MK-3475) or placebo. At a median follow up of 10.5 months, the objective response rate (47.6%, 95% CI, 42.6 to 52.5 vs 18.9% 95% CI, 13.8 to 25.0; P<0.001), progression-free survival (HR 0.52; 95% CI, 0.43 to 0.64; P<0.001) and overall survival (HR 0.49; 95% CI, 0.38 to 0.64; P<0.001) favored the pembrolizumab (MK-3475) arm. The grade 3 or worse adverse event rate was similar in the pembrolizumab (MK-3475)-containing arm vs the placebo containing arm (67.2% vs 65.8%). Furthermore, in the neoadjuvant treatment

of breast cancer, pembrolizumab (MK-3475) has also demonstrated preliminary evidence of activity in combination with chemotherapy (Schmid, 2017). Patients received chemotherapy in 2 different cohorts: Cohort A received single-dose pembrolizumab (MK-3475) followed by 4 cycles of pembrolizumab (MK-3475) Q3W + nab-paclitaxel weekly followed by 4 cycles of pembrolizumab (MK-3474) + doxorubicin + cyclophosphamide Q3W. Cohort B treatment was the same as in A but with carboplatin Q3W added to pembrolizumab (MK-3475) + nab-paclitaxel. The ORR (CR+PR) before surgery was 80% (90% CI, 49-96) with a pathologic complete response rate of 70% (90% CI, 39-91) in cohort A. The ORR (CR+PR) before surgery was 100% (90% CI, 74-100) with a pathologic complete response rate of 90% (90% CI, 61-100) in cohort B.

These data are further supported by the I-SPY2 trial, which evaluated pembrolizumab (MK-3475) in combination with 12- weekly cycles of paclitaxel followed by 4 cycles of adriamycin and cyclophosphamide prior to surgery for high-risk, locally advanced breast cancer (Nanda, 2017). The pathologic complete response rate was tripled with chemotherapy in combination with pembrolizumab (MK-3475) (60%) in triple-negative breast cancer versus chemotherapy without pembrolizumab (MK-3475).

Taken together, these preclinical and clinical observations in other tumor types support the safety and efficacy of checkpoint inhibitors in combination with a cytotoxic chemotherapy backbone (paclitaxel and carboplatin) in patients with advanced stage or recurrent endometrial cancer.

The efficacy of immune checkpoint inhibition in the treatment of solid malignancies is well established, with United States Food and Drug Administration (FDA) approval in multiple disease sites. Furthermore, the clinical utility of checkpoint inhibition in patients with dMMR or MSI-H solid tumors has been documented, with the first ever disease site agnostic FDA approval of pembrolizumab (MK-3475) in patients with unresectable or recurrent tumors progressing after prior therapy who harbor this biomarker. Given the above, we aim to explore whether pembrolizumab (MK-3475) is broadly useful as an immune-oncologic agent for all women with endometrial cancer or more efficacious in the dMMR/MSI-H population. Thus, we will conduct a randomized, placebo-controlled phase III trial, designed to assess the efficacy and safety of pembrolizumab (MK-3475) in combination with paclitaxel and carboplatin versus placebo plus paclitaxel and carboplatin in women with measurable stage III or IVA, stage IVB or recurrent endometrial cancer.

We predict that the addition of pembrolizumab (MK-3475) will improve the efficacy of paclitaxel and carboplatin in advanced stage and recurrent endometrial cancer patients with acceptable toxicity and an associated improvement in quality of life. The primary end point of the randomized phase III trial is progression free survival (PFS). MMR status, for the purpose of stratification, will be determined via centralized tissue testing, and this data will be used to examine the correlation between institutional and central MMR results. The trial will be stratified by dMMR/MSI-H versus MSS/MMR proficient (based on centralized MMR IHC), performance status (0 or 1 versus 2) and receipt of prior adjuvant chemotherapy.

2.3 Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) has high affinity and potent receptor-blocking activity for the programmed cell death 1 (PD-1) receptor, based on preclinical *in vitro* data (Investigator's Brochure, 2018). Pembrolizumab (MK-3475) has an acceptable preclinical safety profile and is being advanced for clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis *et al.*, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as melanoma (Dudley *et al.*, 2005; Hunder *et al.*, 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 [PD-L1] and/or programmed cell death ligand 2 [PD-L2]) (Greenwald *et al.*, 2005; Okazaki *et al.*, 2001).

The structure of murine PD-1 has been resolved (Zhang *et al.*, 2004). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP 1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Chemnitz *et al.*, 2004; Sheppard *et al.*, 2004; and Riley, 2009). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry *et al.*, 2005; Francisco, 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in endometrial cancer.

2.3.1 Pembrolizumab (MK-3475) Background and Clinical Trials

Pembrolizumab (MK-3475), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co. for the treatment of cancer. Pembrolizumab (MK-3475) is approved for treatment of melanoma in several countries; in the United States (US) and European Union it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab (MK-3475) has also been approved for treatment of NSCLC in several countries; in the US it is indicated for use: 1) in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations; 2) in combination with carboplatin and either paclitaxel or nab- paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC; 3) as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA- approved test, with no EGFR or ALK genomic tumor aberrations; and 4) as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab (MK-3475).

Pembrolizumab (MK-3475) is approved in the US for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy, as well as classical Hodgkin Lymphoma (cHL), Primary Mediastinal Large B-Cell Lymphoma (PMBCL), urothelial carcinoma, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma (MCC), and microsatellite instability-high cancer (treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment

Ongoing clinical trials are being conducted in a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure (2018).

2.3.2 Rationale for Pembrolizumab (MK-3475) Dose Selection **(14-OCT-2020)**

The dose of pembrolizumab (MK-3475) planned to be studied in this trial is 200 mg administered every 3 weeks (Q3W) in the combination phase of the clinical trial, and 400 mg administered every 6 weeks (Q6W) in the maintenance setting. The maintenance dose is based on pharmacokinetic modeling and exposure-response analyses that compared the predicted exposure of pembrolizumab 400 mg every six weeks to observed exposures of pembrolizumab in patients who received pembrolizumab at 2 mg/kg every three weeks, 200 mg every three weeks, and 10 mg/kg administered every two weeks. The pharmacokinetic modeling were supported by additional exposure-response analyses across the pembrolizumab development program and an interim analysis of pharmacokinetics and

overall response rate (ORR) in a cohort of patients (Cohort B) enrolled in Study KEYNOTE-555 (NCT03665597). Cohort B of Study KEYNOTE-555 was an international, single-arm, multi-center study that enrolled 101 patients with advanced or metastatic melanoma who had not received prior PD-1, PD-L1, or CTLA-4 inhibitors (other than CTLA-4 inhibitors in the adjuvant setting). The ORR was 39% (95% CI: 24, 55) in the first 44 patients enrolled in KEYNOTE-555 (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-new-dosing-regimen-pembrolizumab).

The initial phase 1 study of pembrolizumab (MK-3475), KN001, evaluated 5 dose levels (1 mg/kg every 2 weeks [Q2W], 3 mg/kg Q2W, 10 mg/kg Q2W, 2 mg/kg Q3W, and 10 mg/kg Q3W) in patients with advanced solid tumors. All 5 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. Pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. In addition, 2 randomized cohort evaluations of melanoma patients receiving pembrolizumab (MK-3475) 2 mg/kg or 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W or 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of any important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab (MK-3475) exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

The PK profile of pembrolizumab (MK-3475) is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. The PK properties of pembrolizumab (MK-3475), specifically the weight-dependency in clearance and volume of distribution, are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in patients with melanoma can be expected. As the antitumor effect of pembrolizumab (MK-3475) is driven through immune system activation rather than through a direct interaction with tumor cells, it is rendered independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses across tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose during the combination phase of the study.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

2.4 Incorporation of maintenance pembrolizumab (MK-3475)/placebo (14-OCT-2020) (08-DEC-2020)

The proposed study will incorporate maintenance pembrolizumab (MK-3475)/placebo for up to 24 months of therapy. The rational for maintenance is based on prior studies conducted in patients with solid malignancies. CheckMate 012, Keynotes 021 and 189 were designed with maintenance checkpoint inhibitor until disease progression or unacceptable toxicity, or up to 24 months of therapy. Furthermore, Keynote 045 (NCT02256436), and Keynote 028 (NCT02054806) were designed to treat with single agent pembrolizumab (MK-3475) until disease progression, toxicity, or until the patient/investigator elected to stop treatment. With respect to front line studies in combination with chemotherapy, Keynote 189 (NCT02578680) and Keynote 407 (NCT02775435) examined pembrolizumab (MK-3475) + chemotherapy, followed by pembrolizumab (MK-3475) maintenance. Specifically, in Keynote 407, subjects will receive up to 35 cycles of pembrolizumab (MK-3475). Based on the above trial designs, the rational exists to adopt an analogous schema in this front-line endometrial cancer study, in an effort to improve clinical response and prolong survival.

A one year period of treatment has been evaluated in adjuvant therapy trials in melanoma and lung cancer. Keynote 054 – resected stage III melanoma (https://www.nejm.org/doi/full/10.1056/NEJMoa1802357) and Checkmate 238 – resected stage III or IV melanoma (https://www.nejm.org/doi/full/10.1056/NEJMoa1709030); showed recurrence free survival benefit (it is unclear as to whether these results will translated into a survival benefit). In stage III lung cancer, adjuvant durvalumab for 1 year after chemoradiation improved overall survival (https://www.nejm.org/doi/full/10.1056/NEJMoa1809697).

The NRG Oncology GY018 study is a trial of advanced/recurrent or metastatic disease and excludes the adjuvant stage III/IVA population (chemotherapy naïve). We therefore chose the up to approximately 24 months of therapy used in comparable patient populations.

NRG Oncology GY018 was amended to incorporate Q6 week pembrolizumab dosing in the maintenance phase as outlined in section 2.3.2 above. This has the advantage of 1) reducing the number of visits required to the infusion center by half for both study arms and 2) reflecting an up to date usual care option that may be employed at the time of trial completion and reporting of results.

Management of potential subject crossover and inclusion of saline placebo (07/03/2019)

With FDA approval of single agent pembrolizumab (MK-3475) in dMMR or MSI-H and FDA accelerated approval of pembrolizumab (MK-3475) plus lenvatinib in patients with pMMR recurrent endometrial cancer, we anticipate the potential for crossover at the time of disease progression for patients randomized to the placebo arm of the trial (details of unblinding are outlined in section 5.2). The use of a saline placebo in combination with standard chemotherapy will help ensure the objectivity of investigator-assessed progression as well as any decisions to interrupt/discontinue therapy, thus preserving the integrity of the

trial and the primary end point of progression free survival (PFS). The timing of scans will be carefully specified and continue after the patient goes off of therapy or until disease progression. Furthermore, disease progression will be assessed using blinded independent central radiology review per RECIST 1.1. Post progression therapy will be monitored for all subjects on study.

The feasibility of a saline placebo in this setting has been established in the recently published, analogously designed, Keynote 189 trial. In this prospective, randomized, double-blind phase 3 clinical trial, patients with metastatic nonsquamous NSCLC received pemetrexed and a platinum-based drug plus either pembrolizumab (MK-3475) or placebo every 3 weeks for 4 cycles, followed by pembrolizumab (MK-3475) or placebo for a total of 35 cycles. Saline placebo was administered as a 30-minute IV infusion every 3 weeks.

The subjects, the investigators and the sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the subjects will be unaware of the group assignments. The chemotherapy agents will be open-label. The sponsor, investigator and subject will not know whether the treatment administered contains pembrolizumab (MK-3475) or saline placebo. Each study site will have an unblinded pharmacist that will obtain each subject's study identification number, and drug assignment and then prepare the solutions for infusion. The unblinded pharmacist will provide the investigative staff with the ready-to-use blinded pembrolizumab (MK-3475)/saline infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits.

Inclusion of MMR-proficient and non-endometrioid histologies

Based on historical data abstracted from prior NRG/GOG clinical trials in this setting, we predict that enrollment on study will consist of: 1/3 grade 1 or 2 endometrioid, 1/3 grade 3 endometrioid and 1/3 serous histologies, with a small proportion of clear cell carcinomas. It is anticipated that robust responses will be identified in the dMMR or MSI-H cohort with the addition of pembrolizumab (MK-3475) to standard chemotherapy. Given that ~ 70% of patients will be microsatellite stable (MSS), we feel that it is important and timely to explore the therapeutic implications of combination checkpoint inhibition + cytotoxic chemotherapy in these patients, irrespective of histology (endometrioid, serous and clear cell). Based on unpublished data from GOG 86P, we anticipate that approximately 40% of patients with recurrent endometrioid adenocarcinoma will be MMR deficient. Conversely, in the serous and clear cell population, MMR deficiency was identified in less than 5% of subjects.

The state-of-the-science argues for such an approach, with 5 current randomized phase III clinical trials exploring chemotherapy +/- checkpoint inhibition in serous histology gynecologic cancers. Furthermore, the recent accelerated approval of pembrolizumab (MK-3475) + chemotherapy as a frontline treatment for patients with metastatic or advanced NSCLC, regardless of PD-L1 expression, supports the assessment of this regimen in patients with recurrent endometrial cancer, where there are limited therapeutic options. As previously published, cytotoxic chemotherapy is immunogenic, and our intent is to determine if pembrolizumab (MK-3475) + chemotherapy results in improved PFS in these patient cohorts (MSS). Furthermore, the potential role of the immune micro environment on endometrial cancer outcomes has been reported, with high numbers of CD8+ T-lymphocytes, and a high CD8+/FoxP3+ ratio being associated with favorable prognostic parameters, and oncologic

outcome across endometrial cancer histotypes.

Assessment of MMR status (03-MAR-2022)

Subject stratification, on trial, will require MMR IHC testing (known stratification factor). With the recent FDA approval of pembrolizumab (MK-3475) in dMMR or MSI-H solid tumors (based on either IHC or PCR), we will look to explore the clinical relevance and reliability of local/institutional testing in this patient population. Therefore, a retrospective, centralized assessment of subjects will be conducted comparing centralized MMR IHC to local MMR IHC. This planned central assessment will be conducted to assess concordance between institutional and centralized determination of MMR IHC status.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Oncology Statistics and Data Management Center-Pittsburgh Office (see protocol cover page).

Inclusion of Women and Minorities (09/24/2019)
NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see
http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Submission of tumor tissue is required for all patients. Investigators should check with their Pathology Department regarding release of tissue biospecimens before approaching patients about participation in the trial. (See Sections 5.7 and 10 for details.)

3.2 Eligibility Criteria (07-FEB-2020) (21-MAY-2021) (09-MAR-2022)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

This is a 2-step registration trial. Consent must be signed BEFORE Step 1 Registration and submitting tissue for centralized MMR IHC testing (see Appendix VIII).

Patients must start treatment within 14 days of randomization.

Drug shipment times must be considered when scheduling a patient for initial treatment (See Section 9.2.4).

3.2.1 Measurable stage III, measurable stage IVA, stage IVB (with or without measurable disease) or recurrent (with or without measurable disease) endometrial cancer.

Pathology report showing results of institutional MMR IHC testing. (Sites in Japan—see Appendix XIV.) **(08-DEC-2020) (09-MAR-2022)**

Histologic confirmation of the original primary tumor is required (submission of pathology report(s) is required). Patients with the following histologic types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, dedifferentiated/undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.). **(07/03/2019)**

Submission of tumor specimens for centralized MMR IHC testing is required after Step 1 and before Step 2 registration. (See Section 5.7 and 10.2 for details.)

3.2.2 In patients with measurable disease, lesions will be defined and monitored by RECIST v 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT or MRI. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI. **(21-MAY-2021)**

3.2.3 Prior Therapy: **(09/24/2019) (07-FEB-2020) (09-MAR-2022)**

- Patients may have received
  - NO prior chemotherapy for treatment of endometrial cancer OR
  - Prior adjuvant chemotherapy (e.g., paclitaxel/carboplatin alone or as a component of concurrent chemotherapy and radiation therapy [with or without cisplatin]) provided adjuvant chemotherapy was completed ≥ 12 months prior to STEP 2 registration.
- Patients may have received prior radiation therapy for treatment of endometrial cancer. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para aortic radiation therapy, intravaginal brachytherapy, and/or palliative radiation therapy. All radiation therapy must be completed at least 4 weeks prior to STEP 2 registration.
- Patients may have received prior hormonal therapy for treatment of endometrial cancer. All hormonal therapy must be discontinued at least three weeks prior to STEP 2 registration.

- Interval or cytoreductive surgery, after start of treatment on this trial, and prior to documentation of disease progression, is NOT permitted**.**

3.2.4 Age ≥ 18

3.2.5 Performance Status of 0, 1 or 2 (see Appendix II) **(07/03/2019)**

3.2.6 Adequate hematologic function defined as follows:

- Platelets ≥ 100,000/mcl
- Absolute neutrophil count (ANC) ≥ 1,500/mcl

3.2.7 Adequate renal function defined as follows: **(07/03/2019)**
Creatinine ≤ 1.5 x institutional/laboratory upper limit of normal (ULN).

3.2.8 Adequate hepatic function defined as follows:

- Total serum bilirubin level ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
- AST and ALT ≤ 3 x ULN

3.2.9 TSH within normal limits. If TSH is not within normal range despite no symptoms of thyroid dysfunction, normal Free T4 level is required. **(09-MAR-2022)**

3.2.10 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of Step 2 registration are eligible for this trial.

3.2.11 For patients of child bearing potential: negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required. **(07-FEB-2020)**

3.2.12 Administration of study drugs (pembrolizumab [MK-3475], paclitaxel, carboplatin) may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of childbearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from at least 14 days prior to Step 2 registration (for oral contraceptives), during treatment, and for 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. Patients will be considered of nonreproductive potential if they are either:

1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient); OR
2) Have a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to Step 2 registration; OR
3) Have a congenital or acquired condition that prevents childbearing. **(07/03/2019)**

3.2.1.3 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. **(07/03/2019)**

3.2.14 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Patients with prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibody or other similar agents.

3.3.2 Patients who have a history of a severe hypersensitivity reaction to monoclonal antibody or pembrolizumab (MK-3475) and/or its excipients; and/or a severe hypersensitivity reaction to paclitaxel and/or carboplatin. **(07/03/2019) (21-MAY-2021)**

3.3.3 Patients who are currently participating and receiving cancer-directed study therapy or have participated in a study of an investigational agent and received cancer-directed study therapy within 4 weeks prior to Step 2 registration. **(07-FEB-2020)**

3.3.4 Patients who have a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to Step 2 registration **(07-FEB-2020)**

- Patients who have received steroids as CT scan contrast premedication may be enrolled.
- The use of inhaled or topical corticosteroids is allowed.
- The use of mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- The use of physiologic doses of corticosteroids may be approved after consultation with the study chair.

3.3.5 Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression, and they have been off steroids for at least 4 weeks prior to Step 2 registration and remain clinically stable. **(07-FEB-2020)**

3.3.6 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. This includes, but is not limited to, patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome because of the risk of recurrence or exacerbation of disease.

Patients with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible.

Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.3.7 Patients who have a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

3.3.8 Uncontrolled intercurrent illness including, but not limited to: ongoing or active infection (except for uncomplicated urinary tract infection), interstitial lung disease or active, non-infectious pneumonitis, symptomatic congestive heart failure, unstable angina pectoris,

cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. **(09/24/2019)**

3.3.9 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; and cirrhosis.

For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.3.10 Pregnant or lactating patients (See Section 3.2.12 for information on contraception and pregnancy).

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 PRE-TREATMENT ASSESSMENTS (09/24/2019) (07-FEB-2020) (14-OCT-2020) (08-DEC-2020) (09-MAR-2022)

Assessments (See Section 10.4.1 for Mandatory Biospecimen Submission Information)	**Prior to Step 1 Registration**	**Prior to Step 2 Registration (calendar days)**	**Prior to Treatment (calendar days) (Cycle 1, Day 1)**
Pathology report confirming endometrial cancer	X		-
Pathology report with institutional mismatch repair protein immunohistochemistry results (MLH1, MSH2, MSH6, PMS2) *As of August 17, 2022, the dMMR cohort is Closed* **(30-SEP-2022)**		X (not required for sites in Japan; Sites in Japan, see Appendix XIV)	-
SLIDE SUBMISSION FOR Centralized mismatch repair protein immunohistochemistry (IHC) (MLH1, MSH2, MSH6, PMS2) and PD-L1 IHC (See Sections 5.7 and 10.2)		X[1]	-
History and Physical		≤ 14 days	≤ 14 days
Concomitant Medications		≤ 14 days	≤ 14 days
Vital Signs		≤ 14 days	≤ 14 days
Performance Status		≤ 14 days	≤ 14 days
Toxicity Assessment		≤ 14 days	≤ 14 days
CBC/Differential/Platelets		≤ 14 days	≤ 14 days
Chemistries*		≤ 14 days	≤ 14 days
TFTs (TSH and Free T4**)		≤ 28 days	≤ 28 days
Hepatitis B Surface Antigen		≤ 28 days	≤ 28 days
Hepatitis B Core Antibody, Total		≤ 28 days	≤ 28 days
Hepatitis C Antibody		≤ 28 days	≤ 28 days
Pregnancy Test (if childbearing potential exists)		≤ 14 days	≤ 72 hours
ECG		≤ 3 months	≤ 3 months
Radiographic Tumor Measurement***		≤ 28 days	≤ 28 days
Patient Reported Outcomes (PRO) *for pMMR patients only*			Baseline – prior to any premedication or treatment administration

[1] Submission of slides to NeoGenomics AFTER Step 1 registration is completed—see Sections 5.7, 10.2 and Appendix VIII.

* Chemistries: BUN/UREA, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT **(21-MAY-2021)**

** Free T4 can be omitted if TSH normal

*** Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to establish the location and extent of disease. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline (and subsequent assessments). Contrast CT is the preferred modality. PET/CT is NOT to be used for any disease assessment or reassessment. Images from radiographic studies should be uploaded for independent radiologic review via TRIAD Digital Image Submission as detailed in Appendix VII.

4.2 ASSESSMENTS DURING TREATMENT (09/24/2019) (14-OCT-2020)

Assessments	Prior to Each Cycle, Day 1 (after Cycle 1, Day 1)	Prior to every other cycle (prior to cycle 3, 5, 7, etc)	Timed (Treatment Cycle Independent)
History and Physical[5]	≤ 3 days **(07/03/2019)**		
Concomitant Medications	≤ 3 days		
Vital Signs	≤ 1 day		
Performance Status	≤ 3 day		
Toxicity Assessment	≤ 1 days		
CBC/Differential/Platelets	≤ 3 days		
Chemistries[1]	≤ 3 days		
TFTs (TSH and Free T4[2])		≤ 3 days	
Radiographic Tumor Measurement			X[3]
Patient Reported Outcomes (PRO) for pMMR patients			X[4]

[1] Chemistries: BUN/UREA, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT **(21-MAY-2021)**

[2] Free T4 can be omitted if TSH normal

[3] Every 9 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) for the first 9 months; then every 12 weeks (+/- 14 days) thereafter. Radiographic tumor measurements are obtained until disease progression is confirmed; at the investigator's discretion, they can be repeated any other time if clinically indicated based on symptoms of physical signs suggestive of new or progressive disease. Utilize **same** imaging modality of abdomen, pelvis and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. **PET/CT is NOT to be used for any disease assessment or reassessment.** Images from radiographic studies should be uploaded for independent radiologic review via TRIAD Digital Image Submission as detailed in Appendix VII. An excel tool is available on the CTSU website to calculate dates of re-imaging.

[4] PROs assessment intervals to occur Week 0, Week 6, Week 18, Week 30, Week 54 (See Section 11.1 Assessment Intervals). PRO assessments are required, even after a patient has been removed from treatment. See Section 11.1.

[5] While on maintenance therapy with placebo or pembrolizumab, patients should be seen every 6 weeks for history and physical exam. During combination treatment (chemotherapy + placebo/pembrolizumab) patients should be seen prior to each cycle of treatment.

4.3 ASSESSMENTS IN FOLLOW UP

Assessments	Timed
Vital Status	1
Toxicity Assessment	2
Radiographic tumor measurement	3

1 Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5-year follow-up period or until study termination, whichever occurs first.

2 Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, see Section 7.

3 In the case that protocol-directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment (until disease progression documented by RECIST 1.1 or until patient initiates a subsequent cancer therapy).

Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Randomization will be stratified within the following groups:

1. Mismatch repair deficient (dMMR) (yes/no) *As of August 17, 2022, the dMMR cohort is Closed* **(30-SEP-2022)**
2. Performance Status (0 or 1 vs 2)
3. Prior chemotherapy (yes/no)

Treatment must begin within 14 days of Step 2 randomization. (07-FEB-2020)

On February 6, 2023, all patient treatment assignments were unblinded and made available through Medidata Rave. Patients randomized to Arm 1 will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol. Patients on Arm 2 will continue all study related treatments and evaluations. **(24-FEB-2023)**

5.1 Treatment (14-OCT-2020) (08-DEC-2020) (19-MAY-2022)

See Appendix III – Carboplatin dose calculation instructions
See Appendix IV – General treatment guidelines

Order of drug administration: pembrolizumab (MK-3475)/placebo, paclitaxel, carboplatin

Arm 1:
Combination Phase:
Placebo over 30 minutes (-5min/+10 min) IV Day 1
Paclitaxel 175 mg/m^2 IV over approximately 3 hours Day 1
Carboplatin AUC 5 IV over approximately 30-60 minutes Day 1 **(07-FEB-2020)**
Carboplatin, Paclitaxel and Placebo will be administered every 3 weeks for a total of 6 cycles in the combination phase
One cycle = 3 weeks

Maintenance Phase:
Placebo IV over 30 minutes (-5min/+10 min) Day 1
Every 6 weeks for up to 14 cycles
One cycle = 6 weeks
Maximum number of placebo cycles (combination phase + maintenance phase) = 20

Arm 2:
Combination Phase:
Pembrolizumab (MK-3475) 200 mg flat dose IV over 30 minutes (-5min/+10 min) Day 1
Paclitaxel 175mg/m^2 IV over approximately 3 hours Day 1
Carboplatin AUC 5 IV over approximately 30-60 minutes Day 1 **(07-FEB-2020)**
Carboplatin, Paclitaxel and Pembrolizumab will be administered every 3 weeks for a total of 6 cycles in the combination phase.
One cycle = 3 weeks

Maintenance Phase (to begin 3 weeks after last chemotherapy cycle):
Pembrolizumab (MK-3475) 400 mg flat dose IV over 30 minutes (-5 min/+10 min) Day 1
Every 6 weeks for up to 14 cycles
One cycle = 6 weeks
Maximum number of pembrolizumab (MK-3475) cycles (combination phase + maintenance phase) = 20

Any patient who is currently receiving Q3 week pembrolizumab in the maintenance phase should be transitioned to a Q6 week pembrolizumab schedule after discussion with the patient and follow assessment intervals as outlined in the protocol document. Please contact study chair and data manager to confirm treatment schedule and total number of cycles for these patients (as it will vary depending on when in the treatment course the transition is made).

Cycle #	1	2	3	4	5	6	7 **Start Maintenance**	8	9	10	11	12	13	14	15	16	17	18	19	20
Week #	0	3	6	9	12	15	18	24	30	36	42	48	54	60	66	72	78	84	90	96

NOTE: Patients with SD or PR who still have measurable disease at the completion of cycle 6 may continue to receive paclitaxel and carboplatin (with pembrolizumab (MK-3475) or normal saline) up to a total of 10 cycles (if deemed necessary by the treating investigator). Patients who continue with cycles 7-10 will continue with all study assessments as described for Prior to each cycle (cycles 1-6).

For patients receiving **7 cycles** of chemotherapy:

Cycle #	1	2	3	4	5	6	7	8 **Start Maintenance**	9	10	11	12	13	14	15	16	17	18	19	20
Week #	0	3	6	9	12	15	18	21	27	33	39	45	51	57	63	69	75	81	87	93

For patients receiving **8 cycles** of chemotherapy:

Cycle #	1	2	3	4	5	6	7	8	9 **Start Maintenance**	10	11	12	13	14	15	16	17	18	19	20
Week #	0	3	6	9	12	15	18	21	24	30	36	42	48	54	60	66	72	78	84	90

For patients receiving **9 cycles** of chemotherapy:

Cycle #	1	2	3	4	5	6	7	8	9	10 **Start Maintenance**	11	12	13	14	15	16	17	18	19	20
Week #	0	3	6	9	12	15	18	21	24	27	33	39	45	51	57	63	69	75	81	87

For patients receiving **10 cycles** of chemotherapy:

Cycle #	1	2	3	4	5	6	7	8	9	10	11 **Start Maintenance**	12	13	14	15	16	17	18	19	20
Week #	0	3	6	9	12	15	18	21	24	27	30	36	42	48	54	60	66	72	78	84

Treatment Up to 20 total cycles (or approximately 24 months)
Treatment with pembrolizumab (MK-3475)/placebo will continue for up to 20 total cycles (or approximately 24 months), or until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, patient withdraws consent, pregnancy of the patient, noncompliance with trial treatment or procedure requirements, administrative reasons, or unblinded patients receiving placebo during maintenance.

5.2 Unblinding Procedures (14-OCT-2020) (08-DEC-2020) (09-MAR-2022) (24-FEB-2023)

Effective February 06, 2023, all patients have been unblinded. Patients randomized to Arm 1 will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol. Patients on Arm 2 will continue all study related treatments and evaluations.

Emergency Unblinding:
The decision to break the unblinding code based on a serious adverse event must be unexpected for the study drug and related to the study drug or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

Unblinding for subsequent treatment planning upon progression of disease:
Commercial pembrolizumab in combination with commercial lenvatinib is available for second-line therapy for women with MMR proficient disease (pMMR/MSS). Commercial pembrolizumab is available for second-line therapy for women with MMR deficient disease (dMMR/MSI-H). Patients and their physicians may request unblinding at the time of progression to determine if they received pembrolizumab in order to guide subsequent treatment decisions. Study-provided pembrolizumab and/or lenvatinib is not available for subsequent treatments.

Unblinding related to COVID-19 safety concerns for patients in maintenance phase or about to enter maintenance phase:
Unblinding can be requested by the patient and/or the patient's treating physician because of safety concerns related to the COVID-19 pandemic. The patient or treating physician can determine that safety of the patient is potentially compromised by COVID-19 in the patient's local/home area, areas of travel, or the office/treatment center. The patient can request unblinding after discussion with the treating physician. The treating physician must then request unblinding and notify the study PI. The patient should be encouraged to continue pembrolizumab maintenance if so assigned; patients may also elect to withdraw consent for treatment, but in that case, they are strongly encouraged to remain on study follow up. The patient's request is to be respected whether or not the treating physician or study PI agree.

Patients who are unblinded and are determined to have received placebo will enter follow up, but will continue scheduled study visits for exams, radiographic tumor measurements and patient reported outcomes as planned per Tables 4.2 and 4.3. **(21-MAY-2021)**

Unblinding Procedures:
The NRG Oncology SDMC maintains an unblinding service that is in operation 24 hours a day, seven days a week. When unblinding is required, the institution representative (PI or CRA) must telephone the NRG Oncology SDMC office at **412-624-2666** and the institution representative will be referred to the Unblinding Administrator. In order to unblind the study drug assignment, the Unblinding Administrator will ask the institution representative to identify the protocol number, the patient ID number, the patient initials (LFM), and the reason for the unblinding request. In addition, to facilitate the process an email should be sent to Mary Jo Antonelli antonellim@nrgoncology.org stating that they wish to unblind a patient's study drug assignment. The treating physician is to be copied on the email, which is to include the protocol number, patient ID, most recent treatment cycle completed, date of most recent treatment cycle, date of most recent scans and results of those scans (for example, disease progression, stable disease, etc.) and the reason for the request to unblind. After this information has been obtained and the indication for unblinding is confirmed, the site representative will be notified immediately of the patient's treatment assignment and a computer record will be created identifying the patient as having been unblinded.

The institution is still responsible for providing continued follow-up for patients whose treatment assignment has been unblinded on the same schedule as indicated in the study protocol.

5.3 Radiation Therapy
Not Applicable.

5.4 Surgery
Not Applicable.

5.5 Device
Not Applicable.

5.6 Imaging
Diagnostic image collection will be utilized for this study. Images from radiographic studies should be uploaded for blinded independent central review (BICR) of progression free survival via TRIAD Digital Image Submission as detailed in Appendix VII. BICR is a means of independently verifying endpoints.

5.7 Integral Biomarker Assay (09-MAR-2022)
Slides for Centralized mismatch repair protein immunohistochemistry (IHC) and PD-L1 IHC must be submitted prior to Step 2 registration/randomization. (See Section 10.2 for details.) Sites in Japan, see Appendix XIV.

5.8 General Concomitant Medication and Supportive Care Guidelines
For all cycles where paclitaxel is to be administered, it is recommended that a preparative regimen be employed, to reduce the risk associated with hypersensitivity reactions. This regimen should include a standard dose of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an alternate H1blocker), and a

standard dose of antihistamine H2 IV (such as ranitidine or famotidine). Paclitaxel preparative regimen can be altered at the discretion of the treating investigator.

It is anticipated that nausea and vomiting may be a significant side effect of this regimen (due to carboplatin administration). An antiemetic regimen is suggested (per institutional, NCCN and/or ASCO guidelines). Antiemetic regimen can be altered at the discretion of the treating investigator. Use of oral steroids as an antiemetic regimen is permitted during the combination phase of the trial, although consideration should be given to minimize steroid use as much as possible and to employ non-steroid containing regimens wherever possible. **(14-OCT-2020)**

5.8.1 Concomitant Medication

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

5.8.1.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAEs).

5.8.1.2 Prohibited Concomitant Medications/Therapy **(07/03/2019) (09-MAR-2022)**

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab (MK-3475)
- Radiation therapy
- Interval or cytoreductive surgery, after start of treatment on this trial, and prior to documentation of disease progression, is NOT permitted.
- Live vaccines within 30 days prior to the first dose of trial treatment and while

participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or for chemotherapy premedication as part of treatment on trial (see Section 5.8). The use of physiologic doses of corticosteroids may be approved after consultation with the study chair.

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

The list above describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.9 Duration of Therapy (14-OCT-2020) (08-DEC-2020) (09-MAR-2022)

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression
- Unblinding at time of maintenance in patients receiving placebo
- Unblinding for subsequent treatment planning upon progression of disease
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), as described in Section 6
- Any dosing interruption lasting > 9 weeks with the following exceptions:
  - Dosing interruptions > 9 weeks that occur for non-drug-related reasons may be allowed if approved by the Study Chair. Prior to re-initiating treatment in a patient with a dosing interruption lasting > 9 weeks, the Study Chair must be consulted.
    *Tumor assessments should continue as per protocol even if dosing is interrupted.
    *PRO assessments should continue on schedule even if dosing is interrupted—See Section 11.1.
- Patient requires systemic steroid or other immunosuppressive treatment (aside from those required to manage treatment-related side effects, those required for safe administration of paclitaxel per institutional standard, and/or those requiring steroid premedication for IV CT contrast).
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT (14-OCT-2020) (21-MAY-2021)

Agent	Starting Dose	Dose -1	Dose -2
paclitaxel	175mg/m^2	135mg/m^2	110mg/m^2
carboplatin	AUC 5	AUC 4	N/A
pembrolizumab (MK-3475)/placebo	200 mg*	N/A	N/A

* Pembrolizumab (MK-3475)/placebo will be given at 200 mg IV every 3 weeks during the combination phase, when given with chemotherapy. During the maintenance phase, pembrolizumab (MK-3475)/placebo will be given at 400 mg IV every 6 weeks.

In the event that pembrolizumab is held for immune-related adverse events during the combination phase of the study, paclitaxel and carboplatin should be continued per protocol timelines (if clinically appropriate). After resolution of pembrolizumab-associated AE, as detailed in section 6.2, pembrolizumab can be resumed at the next planned treatment cycle.

6.1 Paclitaxel and Carboplatin Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events (07-FEB-2020) (21-MAY-2021)

Subsequent courses of treatment which contain cytotoxic chemotherapy (paclitaxel and/or carboplatin) will not begin (day 1 of each cycle) until the ANC is ≥ 1,000 and the platelet count is ≥ 100,000.

Paclitaxel and carboplatin dose modification and supportive care guidelines can be modified per treating investigator's discretion and/or institutional, NCCN and/or ASCO guidelines.

Filgrastim, pegfilgrastim or biosimilars can be used per treating investigators discretion and/or institutional, NCCN and/or ASCO guidelines.

Dose limiting hematologic toxicities are defined as:

- Febrile neutropenia
- Prolonged grade 4 neutropenia persisting for greater than 7 days
- Grade 4 thrombocytopenia (platelet count <25,000)
- Bleeding associated with grade 3 thrombocytopenia (25,000 to <50,000)

Dose modification for dose limiting hematologic toxicity or cycle delay > 7 days due to hematologic toxicity:

ANC	PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Add filgrastim, pegfilgrastim or biosimilar	Reduce carboplatin one AUC unit (AUC 4)	Reduce paclitaxel one dose level
Yes	Yes	Add filgrastim, pegfilgrastim or biosimilar AND reduce carboplatin one AUC unit (AUC 4)	Reduce paclitaxel one dose level	Reduce paclitaxel one dose level
No	Yes	Reduce carboplatin	Reduce paclitaxel one	Reduce paclitaxel one

		one AUC unit (AUC 4)	dose level	dose level

Note: For patients meeting criteria for dose modification after third recurrence, notify study chair

Peripheral neuropathy: for grade 2 (or greater) peripheral neuropathy:
Hold paclitaxel until recovered to grade 1, then paclitaxel should be reduced one dose level. Chemotherapy can be delayed for a maximum of 3 weeks. If neuropathy does not recover to grade 1, paclitaxel should be omitted from subsequent cycles.

Renal toxicity: Renal toxicity is not expected from paclitaxel and/or carboplatin as a direct complication of chemotherapy in this patient population given the required treatment free interval in the pre-treated population. As such, there are no specific dose modifications for renal toxicity. However, see Appendix IV for carboplatin dose calculation instructions for criteria for recalculation of dose.

Hypersensitivity reaction: In general, the occurrence of a hypersensitivity reaction to paclitaxel and/or carboplatin can be managed with administration of medication to prevent hypersensitivity reactions and/or adjustments in infusion rates, per institutional standards.

If a patient experiences a hypersensitivity reaction to carboplatin, platinum graded challenge or desensitization may be allowed after discussion with the study chair. However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the patient will discontinue this agent.

Severe hypersensitivity reactions to paclitaxel do not have to proceed with a re challenge. It is acceptable to substitute docetaxel or paclitaxel protein-bound particles for injectable suspension in patients who had a reaction to paclitaxel with a failed re-challenge (or not amendable to re-challenge). Institutional guidelines can be used for infusion duration. For Japanese sites, the starting dose and modified doses of docetaxel should be 60-70 mg/m^2.

Agent	Starting Dose	Dose -1	Dose -2
Docetaxel (Taxotere)	75mg/m^2	65mg/m^2	55mg/m^2
Paclitaxel protein-bound particles for injectable suspension (Abraxane)	175mg/m^2	135mg/m^2	110mg/m^2

*If substitution of paclitaxel for Docetaxel or paclitaxel protein-bound particles for injectable suspension (Abraxane) is required for reasons other than hypersensitivity reaction (e.g., drug shortage), contact the study team for review and approval prior to making the substitution. **(09-MAR-2022)**

6.2 Pembrolizumab (MK-3475)/Placebo Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events (24-FEB-2023)

6.2.1 Dose Modifications

Adverse events (both non-serious and serious) associated with pembrolizumab (MK-3475)/placebo exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab (MK-3475)/placebo must be withheld for drug-related toxicities and severe or life-threatening AEs as per the table in Section 6.2.3.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

Modification and toxicity management of infusion reaction related to Pembrolizumab (MK-3475) can be found in Section 6.2.4.

6.2.2 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 6.2.3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab (MK-3475)/placebo.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

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

6.2.3 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab (MK-3475) (24-FEB-2023)

AEs associated with pembrolizumab (MK-3475) exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab (MK-3475) 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 (MK-3475), 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 (MK-3475) and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab (MK-3475) are provided in the table below.

Note that non-irAEs will be managed as appropriate, following clinical practice recommendations.

Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab (MK-3475) **(09/24/2019)**

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab 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 pembrolizumab-treatment.
3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a corticosteroid taper.

irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (*i.e.*, diarrhea, abdominal pain, blood or mucus in stool

	Recurrent Grade 3 or Grade 4	Permanently discontinue	Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	with or without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity 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
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.

	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc*.) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
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) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist

	Grade 3 or 4	Withhold or permanently discontinue [d]	methimazole or carbimazole as needed	
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
	Confirmed SJS, TEN, or DRESS	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 based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

6.2.4 Infusion-Related Reactions **(24-FEB-2023)**

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
		(*e.g.* from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

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; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

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

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

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

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (*e.g.* vasculitis and sclerosing cholangitis).

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

6.2.5 Neurological Toxicities **(24-FEB-2023)**

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  o If event resolves to Grade 1 or better, resume pembrolizumab. [b]
	  o If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
	• For facial paresis:
	  o If event resolves fully, resume pembrolizumab. [b]
	  o If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.

[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue pembrolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.2.6 Criteria to Resume Treatment with Pembrolizumab (MK-3475)/Placebo **(07/03/2019) (14-OCT-2020)**

For non-autoimmune or inflammatory events, patients may resume treatment with pembrolizumab (MK-3475)/placebo when the drug-related AE(s) resolve to ≤ Grade 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Patients with drug-related endocrinopathies (not including drug-related adrenal insufficiency or hypophysitis) adequately controlled with only physiologic hormone replacement may resume treatment after replacement correction and clinically stable

regimen.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the treatment should resume at the earliest convenient point that is within the 9-week period.

If treatment is delayed >3 weeks (9 week maximum between doses), the patient must be permanently discontinued from study therapy, except as specified in Section 5.9 (Duration of Therapy).

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY018 is pembrolizumab (MK-3475), which is being made available under an IND sponsored by DCTD, NCI. Determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.5.1.1 of the protocol.

Commercial Agents

The commercial agents in NRG-GY018 are carboplatin and paclitaxel. In this study, the commercial agents are used in combination with investigational agent; therefore, the expedited adverse event reporting criteria for an investigational agent apply. See the reporting table in section 7.5.1.1 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) for MK-3475 (pembrolizumab, NSC 776864) (27-FEB-2020) (06-OCT-2021) (24-FEB-2023)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for Pembrolizumab (MK-3475).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, December 13, 2022[1]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]	
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
		Endocrine disorders - Other (hypoparathyroidism)	
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
		Hepatobiliary disorders - Other (sclerosing cholangitis)	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Arthritis[2]		
	Back pain		
	Joint range of motion decreased		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (optic neuritis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with Pembrolizumab (MK-3475) who received hematopoeitic stem cell transplants.

Adverse events reported on Pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion[2]; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain[2]; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Adverse Events for Commercial Study Agents
Refer to the package insert for detailed pharmacologic and safety information.

7.5 Expedited Reporting of Adverse Events (09-MAR-2022)
All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://ctepcore.nci.nih.gov/ctepaers/security/login Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP for this study by telephone at 301-897-7497 and to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods
- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days. **(07/03/2019)**
- Supporting source documentation is requested by the IND Sponsor for this study (CTEP/DCTD) and NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-879-7404 and to NRG Regulatory Affairs at 215-854-0716.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.1.1 Expedited Reporting Requirements for Adverse Events

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.5.2 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.3 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.5.4 Secondary Malignancies

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.6 Routine Reporting Requirements for Adverse Events (14-OCT-2020)

All Adverse Events **must** be reported in routine study data submission. AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions. See the Rave-CTEP-AERS integration section and Section 13.3.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (07/03/2019) (14-OCT-2020)

8.1 Investigator and Research Associate Registration with CTEP (24-FEB-2023)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant

contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) – MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) – clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) – other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) – individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**	**AB**
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.2 Cancer Trials Support Unit Registration Procedures (09-MAR-2022) (24-FEB-2023)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of

Exemption Form

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

Requirements for NRG-GY018 Clinical Investigators:

- Each Clinical Investigator must ensure all site personnel complete a protocol-specific training course. Training slides are available on the CTSU web site. The CI must submit a signed Certificate of Review. The Certificate of Review lists all applicable staff and attests their completion of the training. The signed Certificate of Review is then submitted to the Regulatory Submission Portal on the www.ctsu.org members' area website. Once the study is activated, the site CI must attest that new study personnel completed the protocol-specific training course by submitting a revised Certificate of Review.

  No site will be able to enroll until this requirement is met.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM

username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number [NRG-GY018] in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select NRG, and protocol number [NRG-GY018].
- Click on *Documents*, *Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol Specific Requirements for NRG-GY018 Site Registration (21-MAY-2021)

- IRB/REB approved consent (International and Canadian sites only: English and native language versions*) English version must be submitted to NRG Oncology (NRG-GY-Regulatory@nrgoncology.org) for review prior to IRB/REB submission. International and Canadian Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology as described below.

  *Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

  Submitting Regulatory Documents:

  Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

  To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

  Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Delegation of Tasks Log (DTL) (09-MAR-2022) (24-FEB-2023)
Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section of the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

Effective February 6, 2023, all patients were unblinded. Submission and maintenance of a Pharmacy Agreement for unblinded site personnel is no longer required. A new DTL (without the Unblinded Study Personnel task) is available on the CTSU website and must be completed and signed by the site CI.

Canadian sites participating under the Canadian Cancer Trials Group (CCTG), should complete the DTL in CCTG's Roster Interface Program & Participants List Environment (RIPPLE) application when CCTG holds the Clinical Trials Agreement with Health Canada. RIPPLE is integrated with the CTSU DTL application for this trial.

8.3 Patient Enrollment (24-FEB-2023)

8.3.1 Patient enrollment for this **2-step (registration and randomization)** trial will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-(AM accounts and by July 1, 2023 for all users);
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

NOTE: Step 2 registration requires a second web registration for all patients.

8.3.2 KIT ORDERING for Centralized MMR IHC Testing and PD-L1 IHC Testing (09/24/2019) (09-MAR-2022) (19-MAY-2022)

Initial orders of PPD Laboratories' supplies can be requested by the site user via the web application, **PPD Lab Supply Registration**, available at https://apps.nrgoncology.org/LabKitRegistrationApp/PPDLabKitStartPage.aspx. Your CTEP-IAM credentials are required to access the PPD supplies ordering software. Once logged in you will be able to order supplies for any site you are affiliated with on the NRG Oncology roster.

To order your supplies, your site must first be approved to request PPD supplies through this application. Approvals are processed by NRG Oncology Regulatory staff and access to the PPD supply ordering software will be granted 24-48 hours after your site has satisfied the

following requirements:

- IRB approval
- DTL approval
- NRG-GY018 Certificate of Review for protocol training for all staff listed on DTL

- Signed Pharmacy AgreementWhen ordering your initial supply via this application, site address and contact details are requested. Please use this application to keep your site and contact details up to date to ensure proper and timely delivery. Additional supply orders should be made through the PPD Laboratories Preclarus portal. Individual e-mail links will be sent from PPD Laboratories to each site after the initial kit order.

There is a 14 business day turnaround time (from the day your supply is requested from PPD Laboratories) to receive the MMR and PD-L1 IHC testing supplies. **There is no expedited shipping.**

PPD will provide the following in your initial shipment:

Print Proforma | Document Repository | Preview Order | Print Order | Back To Orders

Item	PPD Part Number	Cat Number	Pack Config	Units	Exp / Lot #	Back Order	Qty
AWB-FEDEX US Ambient a/o Refrigerated NEOGENOMICS LAB	N/A	WB-645	Each	Each			15
Box-Refrigerated Shipper	10004417	PPD-RS	Each	Each			5
Courier Contact Sheet-FEDEX-NEOGENOMICS LAB	N/A	C-61	Each	Each			15
Form-MERCK TISSUE REQUEST FORM	N/A	FL-800	Each	Each			1
Gel Pack-Ambient Shipper Gel Wrap White/Clear	10004522	PPD-GEL	Each	Each			15
Letter-REFRIGERATED SHIPMENT	N/A	FL-REFRIGERATED-SHIPMENT	Each	Each			1
Slide-Empty Mailer Holds 25 (Light Sensitive)	10008041	513075A	Each	Each			6
Slide-Super Frost Plus	10013890	48311-703	Package of 72	Pack	20905-687257		1

For any related questions or concerns please contact NRG-GY-Regulatory@nrgoncology.org.

8.3.3 Summary of Registration Procedures **(21-MAY-2021) (09-MAR-2022)**

This is a 2-step registration study.

- All eligibility criteria, as determined by pre-screening and patient's medical history/pathology report, must be met prior to Step 1 registration. (No assessments per Sec 4.1 need to be completed prior to Step 1.)
- All patients will be registered to Step 1.
  - Slide submission is required for the central MMR IHC and PD-L1 IHC after Step 1 registration has been completed and a case number has been assigned. (Refer to Section 10.2 and Appendix VIII for details on tissue submission.)
- After slides are sent to Neogenomics for centralized testing, patients can be registered to Step 2. Sites do not have to wait for central testing results to return. (Sites in Japan, see Appendix XIV.)

8.4 Data Submission / Data Reporting (09/24/2019) (09-MAR-2022) (24-FEB-2023)

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen ; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name. **(07-FEB-2020)**

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data

Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

Central Monitoring (CM) (24-FEB-2023)

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP) application. This application is also available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with any of the Rave roles on a relevant site roster can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU SDP application under Browsering > Document Repository in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

Please see Section 13.3.

Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period, and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event Form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules

evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence, that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event* Reporting; and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics.*

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and

unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

8.5 Agent Ordering and Agent Accountability (09-MAR-2022) (24-FEB-2023)

8.5.1 NCI-supplied agents may be requested by authorized designees on behalf of eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number and subject ID number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF).

No starter supplies will be available for this study. The initial patient specific clinical supplies will be sent to the pharmacy shipping address of the registering investigator at the time of randomization and should arrive within approximately 5 to 7 days. (Section 9.4.5)

Patients Randomized to Pembrolizumab (MK-3475)
The initial request will be submitted automatically following the completion of patient registration and randomization. Subsequent patient-specific agent supply requests may only be submitted through the PMB AURORA application. Access to AURORA requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Patients Randomized to Placebo

The initial request will be submitted automatically following the completion of patient registration and randomization. The initial shipment will contain an empty patient-specific carton containing a memo identifying the subject ID as being randomized to placebo and detailing how placebo infusions are to be compounded. No saline vials will be included.

As of amendment 9 (version date 09-MAR-2022), all patients randomized to placebo will have their placebo infusions prepared using stock supplies from the site. Pembrolizumab placebo (saline) vials will no longer be available to order through the OAOP application.

8.5.2 Investigator Brochure Availability

The current version of the pembrolizumab (MK-3475) IB will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "Current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.5.3 Agent Accountability (24-FEB-2023)

The investigator, or a responsible party designated by the investigator must maintain a careful record of the agent receipt, dispensing and final disposition of all agents received from the PMB using the NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page.

Maintain separate NCI Investigational Agent Accountability Records for each study participant and ordering investigator on this protocol. Once the final blinded pembrolizumab vials are removed from inventory, the DARF should be closed by marking an 'X' through the remaining lines on the page. A new patient-specific DARF should be started to record unblinded pembrolizumab vials. The manufacturer, lot number and expiration date from the vial labels are to be recorded on the unblinded DARF.

As of February 6, 2023, all patients have been unblinded. Once blinded supplies have been exhausted, blinded DARFs should be closed out and new patient-specific DARFs should be started for any patient continuing on open label treatment. Blinded DARFs should be retained for future auditing purposes.

8.5.4 PMB Useful Links and Contacts (07/03/2019) (24-FEB-2023)

- *CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/*
- *NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov*
- *PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm*
- *PMB AURORA application:* https://ctepcore.nci.nih.gov/aurora
- *CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp*
- *CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov*
- *IB Coordinator: IBCoordinator@mail.nih.gov*
- *PMB email: PMBAfterHours@mail.nih.gov*
- *PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)*

8.6 ePRO Registration Process (07/03/2019)

8.6.1 Medidata Patient Cloud ePRO **(21-MAY-2021)**

This study includes the use of Medidata Patient Cloud ePRO, (electronic patient-reported outcomes). After the patient is registered to the trial via OPEN, and if the patient can read or understand English, French, or Spanish, the site staff will complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed eLearning for the Patient Cloud ePRO application to register a patient. Information about the training is in Appendix XII. The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the

Patient Cloud ePRO app onto his/her own device (IOS, Android, phone, or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient-reported outcomes electronically for the trial.

For sites providing a shared institutional device for use by multiple patients on site: The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

If a patient prefers paper-based survey or using phone/tablet is not possible at the scheduled time, a paper questionnaire should be provided for the patient to complete manually. The questionnaires can be found on the CTSU website.

Sites in Japan and Korea will use paper-based PRO surveys.

8.6.2 CRA Patient Registration Instructions for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study.
ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject is added and will include the date the patient was added, the subject ID, subject initials (if included), and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered, the status will change from "invited" to "registered".

Reminder – site staff must have already completed the Medidata Patient Cloud training in order to register study participants. Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

9. DRUG INFORMATION

9.1 Investigational Study Agent: pembrolizumab (MK-3475) (NSC# 776864) /CTEP-supplied placebo (14-OCT-2020) (09-MAR-2022)

9.1.1 Other Names: Pembrolizumab, SCH 900475, KEYTRUDA®

Classification: Anti-PD-1 MAb

Molecular Weight: 148.9-149.5 KDa

CAS Number: 1374853-91-4
Mode of Action: The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. MK-3475 blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands.

9.1.2 Description: Pembrolizumab (MK-3475) is a humanized MAb of the IgG4/kappa isotype.

9.1.3 How Supplied: Pembrolizumab **(**MK-3475) for subjects enrolled to the Active treatment arm is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix V).

Active Agent
Pembrolizumab (MK-3475) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each single dose vial contains 100 mg of pembrolizumab (MK-3475) in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. **(14-OCT-2020)**

Placebo
Site-supplied 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in an infusion bag will be used as Placebo.

9.1.4 Preparation: Pembrolizumab solution for infusion must be diluted prior to administration. Allow vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles are observed. Do not use if discolored. To prepare the infusion solution add 8 mL (200 mg) or 16 mL (400 mg) of pembrolizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final volume must be between **20 mL to 200 mL (1 mg/mL to 10 mg/mL)**.

Pembrolizumab placebo infusions will be prepared using supplies provided by the site. The pembrolizumab placebo infusion can be prepared using 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP in an infusion bag. The final volume must be between 20 mL to 200 mL. To maintain the blind, manage infusion bag injection port(s) as for a

pembrolizumab infusion.
(14-OCT-2020)

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin.
(24-FEB-2023)

9.1.5 Storage: Store provided vials as stated in the protocol and PMB applied box label.

Store intact vials of pembrolizumab between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light. Do Not remove vials from the original carton.

If a storage temperature excursion is identified, promptly return pembrolizumab to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability. **(24-FEB-2023)**

9.1.6 Stability: Stability testing of investigationally labeled pembrolizumab vials is on-going. Commercially labeled pembrolizumab will contain a manufacturer's expiration date on the label. Do not administer past this date. The manufacturers' expiration date from the vial label must be recoded on the UNBLINDED, patient-specific DARF.

Administer prepared solutions of pembrolizumab immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion. **(14-OCT-2020) (24-FEB-2023)**

9.1.7 Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection.

Method of Administration: Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri- (2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Patient Care Implications: Refer to Section 6 for information on evaluation and management of potential immune-related adverse events.

9.1.8 Adverse Events: Please see Section 7.3 for the MK-3475 CAEPR.

9.2 Provision of Pembrolizumab (MK-3475) and Placebo (09-MAR-2022)

9.2.1 Pembrolizumab (MK-3475) will be provided free of charge by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation

Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). Clinical supplies inside the PMB-supplied box are not provided in a blinded fashion. Thus, Unblinded Study Personnel are required to employ efforts throughout the course of the trial to maintain the study blind for enrolled study subjects and other site personnel.

A nationwide shortage of normal saline (placebo) vials has affected Merck's ability to provide the NCI an adequate supply of normal saline vials used as pembrolizumab placebo for this trial. To continue the conduct of this trial, pembrolizumab placebo infusions will be prepared using stock supplies from the site without the addition of saline from PMB . See Section 9.1.4 for preparation instructions and Section 9.2.4 for documentation instructions.

9.2.2 Effective February 6, 2023, the Unblinded Study Personnel (USP) task is no longer required for the NRG-GY018 DTL. A new version of the DTL has been released without the USP task and will need to be completed and signed by the site CI.

For subjects randomized to the Active treatment arm, study agent will be provided in cartons containing eight vials of pembrolizumab. The carton will be tamper-evident-sealed. The vials of pembrolizumab inside the carton will not be blinded. Each vial within the carton will contain an auxiliary label with the patient's study ID number. **(09/24/2019) (24-FEB-2023)**

9.2.3 Each patient-specific carton will be labeled with …

- the protocol number (i.e., "NRG-GY018")
- the total number of vials per box (i.e., "8 vials")—**Pembrolizumab shipments only (21-MAY-2021)**
- the patient ID number (e.g.,"AAXXX-GY018-XXXXX", which represents the unique patient identifier assigned at registration)
- the patient initials (i.e., Last initial, First initial, Middle initial [e.g., "L, FM"])
- the agent identification (i.e., "Pembrolizumab 100 mg"
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Dilute in NS or D5W to a final volume between 20-200 mL.")
- storage instructions (i.e., "Store between 2°C - 8°C in the original box. Do not freeze.")
-
- a Julian date

The Julian date indicates the day the vials were labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2019 = 19, 2020 = 20) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2019 would have a Julian date of '19001' and a bottle labeled and shipped on December 31, 2019 would have a Julian date of '19365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all vials (i.e., both Pembrolizumab (MK-3475) and 0.9% sodium chloride) shipped on or before that date.

Once the final blinded pembrolizumab vials are removed from inventory, the DARF should be closed by marking an 'X' through the remaining lines on the page. A new, patient-specific DARF should be started to record unblinded pembrolizumab vials. The manufacturer, lot number and expiration date are to be recorded on the unblinded DARF. **(24-FEB-2023)**

9.2.4 **No starter supplies will be available for this study.** Patient specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 5 to 7 days. This randomization will be performed by the NRG Oncology SDMC. The assigned NRG patient ID number must be recorded by the registering institution. Once a patient has been randomized, the NRG Oncology SDMC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the NRG Oncology SDMC the day the patient is randomized, provided it is before 3PM ET. If the patient is randomized after 3PM ET, the order will be transmitted the next business day. **Orders will be processed by the PMB the next business day after transmission and shipped the following business day.** Orders are not shipped the day before a Federal Holiday. Shipments within the United States will be sent by FedEx Next Day. Shipments to United States sites can be expedited to early morning delivery by the provision of an express courier account name and number to the PMB at the time the patient is randomized. Please note that additional processing time is required for QA/QC checks on patient-specific/blinded orders and **next day delivery is not available**.

Orders to Canadian sites are shipped Monday through Wednesday only.
Orders to Japan and South Korea are shipped on Fridays only.

Please see the chart below for order timelines for shipments to the US:

Drug Order Submitted to PMB*	Drug Order Shipped to Site from PMB	Drug Received at Site
Monday	Tuesday	Wednesday
Tuesday	Wednesday	Thursday
Wednesday	Thursday	Friday
Thursday	Friday	Monday
Friday	Monday	Tuesday

*if received by 2pm ET. **(21-MAY-2021) (24-FEB-2023)**

Patients Randomized to Pembrolizumab (MK-3475)
The initial request will be submitted automatically following the completion of patient registration and randomization. The request will contain 8 vials [a 4 cycle (12 week) supply] of Pembrolizumab (MK-3475) 100 mg vials. At the time the cycle 4 dose is prepared, sites may order an additional 8 vials [a 4 cycle (12 week)] supply using AURORA, the PMB's web-based inventory management system. **Note: Sites must monitor their supply as the pembrolizumab dose increases to 400 mg (4 vials) at maintenance.** The assigned patient ID number (e.g., "AAXXX-GY018-XXXXX") and the patient initials (e.g., "L, FM") should be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., "AAXXX-GY018-XXXXX") being requested. All drug orders will be

shipped directly to the address of the shipping physician as designated upon patient registration. **(14-OCT-2020) (21-MAY-2021) (24-FEB-2023)**

Patients Randomized to Placebo
The initial request will be submitted automatically following the completion of patient registration and randomization. The initial shipment will contain an empty patient-specific carton and a memo identifying the subject ID as being randomized to placebo and detailing how placebo infusions are to be compounded. No saline vials will be included.

As of amendment 9 (version date 09-MAR-2022), all patients randomized to placebo will have their placebo infusions prepared using stock supplies from the site. Pembrolizumab placebo (saline) vials will no longer be available to order through the OAOP application.

Documenting the dispensing of each placebo infusion bag on a patient specific DARF is not required. However, if a patient specific DARF is maintained, it is to be completed per institutional procedures.

All transfers (e.g., from one patient to another patient or from one protocol to another protocol., the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators (or their designee) should complete and submit via email to the PMB a Transfer Investigational Agent Form available on the PMB home page (https://ctep.cancer.gov/branches/pmb/default.htm) or by calling the PMB. The patient ID number (e.g. "AAXXX-GY018-XXXXX"') and the patient initials (e.g. "L, FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e. "NRG-GY018"). In the event of a patient institution transfer, the site to which the patient transferred cannot order study drug until the patient is officially transferred through the CTSU. **(24-FEB-2023)**

Drug Returns
When it is necessary to return undispensed study drug (e.g. sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), US sites must return the study drug to the PMB using the NCI Return Drug List available on the PMB home page or by calling the PMB. The patient ID number (e.g. "AAXXX-GY018-XXXXX") and the patient initials (e.g. "L, FM") should be entered in the "Lot Number" field. When returning unblinded vials, complete the NCI Return Drug List per the instruction of the form. **(21-MAY-2021) (24-FEB-2023)**

Non-US sites will utilize the PMB Local Destruction process. Sites must contact PMB for a copy of the Request for Authorization for Local Destruction form prior to destroying patient-specific supplies. Approval for local destruction must be received prior to vial destruction and should be maintained in the study file for documentation of final agent disposition. **(21-MAY-2021)**

Reporting Errors
If a medication error involves patient-specific supplies (e.g. blinded studies), report the

incident immediately to PMB by calling 240-276-6575 and asking for the pharmacist responsible for the blinded agent supply.

9.3 Commercial Agent: Carboplatin

Please refer to the current FDA- approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.3.1 Product Description

Carboplatin is commercially available. Carboplatin aqueous solution injection is a premixed aqueous solution of 10 mg/mL carboplatin. Dosage forms include **50mg**/5mL, **150 mg**/15mL, **450 mg**/45mL and **600 mg**/60 mL aqueous solution in multidose vials.

9.3.2 Solution Preparation

See the carboplatin package insert for preparation instructions.

9.3.3 Route of Administration **(07/03/2019)**

Carboplatin AUC 5 IV over approximately 30-60 minutes. See Section 5.1. **(07-FEB-2020)**

9.3.4 Agent Ordering

Carboplatin is commercially available.

9.3.5 Adverse Events

Hair loss, Vomiting/Nausea, Infection, Anemia, Bruising/Bleeding, Belly pain, Diarrhea/Constipation, Peripheral Neuropathy, Allergic Reaction.

Please see the Carboplatin package insert for the most current and complete information.

9.4 Commercial Agent: Paclitaxel

Please refer to the current FDA- approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.4.1 Product Description **(21-MAY-2021)**

Paclitaxel is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion Paclitaxel is available in 30 mg (5mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor ® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

9.4.2 Solution Preparation

See the paclitaxel package insert for preparation instructions.

9.4.3 Route of Administration **(07/03/2019)**

Paclitaxel 175 mg/m^2 IV over approximately 3 hours. See Section 5.1.

9.4.4 Agent Ordering

Paclitaxel is commercially available.

9.4.5 Adverse Event List

Neutropenia, Alopecia, Anemia, Arthralgia/myalgia, Diarrhea, Leukopenia, Nausea/Vomiting, Opportunistic infections, Peripheral neuropathy, Thrombocytopenia, Mucositis, Hypersensitivity, Renal impairment, Hypotension.

Please see the paclitaxel package insert for the most current and complete information.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Pathology Review Guidelines

Not Applicable

10.2 Biospecimen Selection for Integral Biomarker Testing (09/24/2019) (21-MAY-2021) (19-MAY-2022)

Formalin-fixed, paraffin-embedded unstained sections for centralized mismatch repair (MMR) immunohistochemistry (IHC). Sections **must** be prepared using the Superfrost slides provided by PPD.

PPD Laboratories will provide the supplies required to collect, prepare, and ship MMR **and** PD-L1 IHC samples for this study.

******Note: There is an approximate 14 day turnaround time between placing a kit request and receiving a kit. Please plan accordingly.******

10.2.1 Integral Biomarker Testing Requirements and Reporting (09-MAR-2022)

Testing Requirements

- All sites must have submitted patient slides for centralized MMR IHC testing prior to Step 2 registration/stratification/randomization. (Sites in Japan, see Appendix XIV.)

Reporting

- MMR IHC results will be reported to the NRG SDMC **(07-FEB-2020)**
- Reporting will consist of proficient (pMMR), deficient (dMMR), or inconclusive. If the result is inconclusive, additional slides may be requested and used until a result is obtained.
- Sites in Japan—see Appendix XIV.

10.2.2 Method of Integral Biomarker Testing

Immunohistochemistry

- MMR IHC Class 2 commercial kit (LDT)
- All specimens will be stained using the VENTANA MMR IHC Panel (Ventana Medical Systems, Inc., Tucson, AZ). Specific components of the VENTANA MMR IHC Panel are listed below. Briefly, 4µm sections on Superfrost plus glass slides will be stained using the OptiView DAB IHC Detection and, for VENTANA anti-PMS2

(A16-4) antibody, OptiView Amplification Kit on the BenchMark ULTRA instrument.
    - The VENTANA MMR IHC Panel includes: VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody, VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody, and VENTANA BRAF V600E (VE1) Mouse Monoclonal Primary Antibody.
- Only a certified pathologist should score samples. Samples should only be scored on glass slides, not from digital scanned images.

10.2.3 Location of Integral Biomarker Testing (09/24/2019)

NeoGenomics Laboratories, Inc., Aliso Viejo, CA

10.2.4 Biospecimen Submission for Integral Biomarker Testing (07/03/2019) (09/24/2019) (07-FEB-2020) (21-MAY-2021) (09-MAR-2022) (19-MAY-2022)

Refer to Appendix VIII for details. Note: Instructions for PD-L1 IHC samples are listed in Biospecimen Submission for Exploratory Biomarker Testing (section 10.5.4).

- **Shipping supplies and instructions will be provided by PPD.** See Section 8.3.2 for details.
    - **Note: There is an approximate 14 business day turnaround time between placing a supply request and receiving a kit. Please plan accordingly.**
- **Nine (4µm, charged) unstained sections** of FFPE primary or metastatic tumor tissue must be submitted for MMR IHC. Sections **must** be prepared using the Superfrost slides provided by PPD.
    - The tumor lesion submitted must not have been previously irradiated.
- Sections should be **fresh cut within 48 hours of shipping** from a block that is less than five years old.
    - A fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow, cytologic specimen, decalcified, or formalin fixed sample that was frozen at any point will not be acceptable for analysis.
    - A minimum of 100 viable tumor cells is required for MMR IHC; otherwise, the sample will be reported as "not evaluable." If possible, samples with greater than 50% tumor cellular content is preferred if available.
- **Each slide must be labeled with two identifiers**. Label each slide with the NRG Patient ID and Block ID (i.e., Surgical Pathology number and block number). Serially number slides in the order they were sectioned with indelible ink. **The same two identifiers must also be included on the Tissue Sample Transmittal Form.**
    - **Failure to include both identifiers on each slide and the Tissue Sample Transmittal Form will result in testing delays.**
- Unstained sections should be shipped directly to NeoGenomics Laboratories, Inc. (address below) **Monday through Thursday only**.
    - Sectioned slides should be shipped refrigerated year round. **Refer to the instructions provided by PPD for additional details.**
    - A completed copy of the Tissue Sample Transmittal Form (a paper version of this

form will be provided by PPD but should only be used when the Rave GY018 EDC System is not available to the site) and corresponding pathology report must be included.
    - Incomplete transmittal forms will cause processing delays.
    - Sites should retain a copy of the completed form for their records.
- Site in Japan—see Appendix XIV.

  NeoGenomics Laboratories, Inc.
  Attn: Pharma Services Dept.
  31 Columbia
  Aliso Viejo, CA 92656
  Email: pharma_project_support_team@neogenomics.com
  Phone: 949-445-7300, x7103

- If the central lab is unable to obtain a result due to technical error and not due to the sample submitted, additional slides may be requested and used until a result is obtained.
- See Appendix VIII for additional details.

10.3 Biospecimen Selection for Integrated Biomarker Testing
Not Applicable.

10.4 Biospecimen Submission Tables
Biospecimens listed below should not be submitted until after patient registration and Bank ID assignment. A detailed description of biospecimen procedures can be found in Appendix VI.

10.4.1 Mandatory Biospecimen Submissions (07-FEB-2020) (21-MAY-2021) (09-MAR-2022)
Not applicable

10.4.2 Optional Biospecimen Submissions (09-MAR-2022)
If the patient gives permission to participate in this optional study component, then participating sites are required to submit the patient's biospecimens as outlined below.

Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship Biospecimens To
FFPE TUMOR TISSUE ***(Submit one of the following – Listed in order of preference)***		
FFPE Persistent Primary Tumor (FPP01) *or* Metastatic Tumor (FPM01)[1] 1st choice: block 2nd choice: 10 unstained slides (charged, 5µm)	Prior to study treatment; lesion must *not* have been previously irradiated	NRG Oncology BB-Columbus within 8 weeks of registration[2] **Sites in Korea:** KGOG central lab within 8 weeks of registration[3] **Sites in Japan:** Central lab within 8 weeks of registration[4]
FFPE Recurrent Primary Tumor (FRP01) *or* Metastatic Tumor (FRM01)[1] 1st choice: block 2nd choice: 10 unstained slides (charged, 5µm)	Prior to study treatment; lesion must *not* have been previously irradiated	
FFPE Primary Tumor (FP01) *or* Metastatic Tumor (FM01)[1] 1st choice: block 2nd choice: 10 unstained slides (charged, 5µm)	Prior to all treatment; lesion must *not* have been previously irradiated	

FFPE Primary Neoadjuvant Tumor (FPT01) *or* Metastatic Neoadjuvant Tumor (FMT01)[1] 1st choice: block 2nd choice: 10 unstained slides (charged, 5µm)	Prior to study treatment; lesion must *not* have been previously irradiated. Only submit if tumor collected prior to any treatment is not available.	
BLOOD BIOSPECIMENS		
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s) and frozen[4]	Prior to study treatment	NRG Oncology BB - Columbus within 1 week of registration[2] **Sites in Korea:** KGOG central lab within 5 weeks of registration[3] **Sites in Japan:** Central lab within 5 weeks of registration[4]

1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-Columbus. **Sites in Korea and Japan** must provide an English translated copy of the corresponding pathology report. Note: The entire report must be translated, typed, and include diagnosis, clinical history, gross description or block number, and microscopic findings.

2 NRG Oncology BB-Columbus / Protocol NRG-GY018, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

3 **Sites in Korea** should ship to the KGOG central lab. The KGOG central lab will batch ship all biospecimens to the US.

4 **Sites in Japan** should ship to the central lab. The central lab will batch ship all biospecimens to the US.

5 Do not use glass blood collection tubes.

10.5 Biospecimen Selection for Exploratory Biomarker Testing (09/24/2019) (21-MAY-2021) (09-MAR-2022) (19-MAY-2022)

Formalin-fixed, paraffin-embedded unstained sections for PD-L1 immunohistochemistry (IHC). Sections **must** be prepared using the Superfrost slides provided by PPD.

PPD Laboratories will provide the **one** kit required to collect, prepare, and ship MMR **and** PD-L1 IHC samples for this study.

*****Note: There is an approximate 14 business day turnaround time between placing a kit request and receiving a kit. Please plan accordingly.*****

10.5.1 Exploratory Biomarker Testing Requirements and Reporting (09-MAR-2022)

Testing Requirements

- All sites must submit patient tumor tissue for PD-L1 IHC. The slides for this testing should be submitted with the slides for MMR IHC testing (12 slides total).

Reporting

- PD-L1 IHC results will be reported back to the NRG SDMC.

10.5.2 Method of Exploratory Biomarker Testing

Immunohistochemistry

PD-L1 22C3 PharmDx IHC assay will be used for assessment of PD-L1 expression. Investigational Use Only (IUO) kits to be provided by Agilent to Neogenomics for assessment of PD-L1 expression. **(07-FEB-2020)**

Assay Performance

Monoclonal mouse anti-PD-L1, clone 22C3, immunoreactivity was tested on a panel of neoplastic tissues including uterine adenocarcinoma (clear cell and endometrium) and squamous cell carcinoma. Plasma membrane staining was observed on immune cells and cells of epithelial origin. Cytoplasmic staining was noted in some cell types but was not recorded as positive staining. There were no unexpected results observed in the tumor biospecimens tested; observed staining was consistent with the reported literature for PD-L1 IHC expression in neoplastic tissues. Clone 22C3 showed no immunoreactivity (plasma membrane staining, cytoplasmic staining, or non-specific staining) in normal uterus tissues.

Scoring

As per manufacturer's instructions, PD-L1 expression using clone 22C3 is determined by Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Theoretically, this score can be greater than 100, although the maximum value is capped at 100. All viable tumor cells on the entire tissue section must be evaluated and included in PD-L1 expression assessment; however, a minimum of 100 viable tumor cells must be present in the PD-L1 stained slide for the biospecimen to be considered adequate for evaluation.

From previously published reports describing the clinical utility of CPS for PD-L1 expression in biospecimens from patients with gastric and gastroesophageal junction adenocarcinoma (Kulangara, et al), external reproducibility assessments demonstrate interpathologist overall agreement of 96.6% (95% CI 94-98.7%) and intrapathologist overall agreement of 97.2% (95% CI 95.3-98.9%). Thus, CPS is a robust, reproducible PD-L1 scoring method, which has been previously evaluated in a pan-tumor manner (e.g., using biospecimens from KEYNOTE-012, -028, and -059). Importantly, the clinical utility of CPS is underscored by the September 2017 FDA approval of pembrolizumab (MK-3475) for treatment of patients with PD-L1 expressing gastric or gastroesophageal junction adenocarcinomas.

10.5.3 Location of Exploratory Biomarker Testing

NeoGenomics Laboratories, Inc., Aliso Viejo, CA

10.5.4 Biospecimen Submission for Exploratory Biomarker Testing (09/24/2019) (07-FEB-2020) (21-MAY-2021) (09-MAR-2022) (19-MAY-2022)

Refer to Appendix VIII for details. Note: Instructions for MMR IHC samples are listed in Biospecimen Submission for Integral Biomarker Testing (section 10.2.4).

- **Shipping supplies and instructions will be provided by PPD.**
- **Three (4µm, charged) unstained sections** of FFPE primary or metastatic tumor tissue

must be submitted for PD-L1 IHC. Sections **must** be prepared using the Superfrost slides provided by PPD.
    - The tumor lesion submitted must not have been previously irradiated.
- Sections should be **fresh cut within 48 hours of shipping** from a block that is less than five years old.
    - A fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow, cytologic specimen, decalcified, or formalin fixed sample that was frozen at any point will not be acceptable for analysis.
    - A minimum of 100 viable tumor cells is required for PD-L1 IHC; otherwise, the sample will be reported as "not evaluable." If possible, samples with greater than 50% tumor cellular content is preferred if available.
- **Each slide must be labeled with two identifiers**. Label each slide with the NRG Patient ID and Block ID (i.e., Surgical Pathology number and block number). Serially number slides in the order they were sectioned with indelible ink. **The same two identifiers must also be included on the Tissue Sample Transmittal Form.**
    - **Failure to include both identifiers on each slide and the Tissue Sample Transmittal Form will result in testing delays.**
- Unstained sections should be shipped directly to NeoGenomics Laboratories, Inc. (address below) **Monday through Thursday only**.
    - Sectioned slides should be shipped refrigerated year round. Refer to instructions provided by PPD for additional details.
    - A completed copy of the Tissue Sample Transmittal Form (a paper version of this form will be provided by PPD but should only be used when the Rave GY018 EDC System is not available to the site) and corresponding pathology report must be included.
        - Incomplete transmittal forms will cause processing delays.
        - Sites should retain a copy of the completed form for their records.

- If the sponsor-designated laboratory is unable to obtain a result due to technical error and not due to the sample submitted, additional slides may be requested and used until a result is obtained.
- See Appendix VIII for additional details.

10.6 Banking Biospecimens for Future Research

Note: Additional integrated or exploratory biomarker testing of banked biospecimens will not occur until an amendment (integrated) to this treatment protocol or separate correlative science protocol (exploratory) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

Details regarding the banking and use of biospecimens for future research can be found in Appendix VI.

11. SPECIAL STUDIES (Non-Tissue)

11.1 Patient Reported Outcomes (PROs) in the pMMR population

1. Quality of Life, as measured by the Functional Assessment of Cancer Therapy – Endometrial Trial Outcome Index (FACT-En-TOI).
2. Fatigue, as measured by the 7-item Patient Reported Outcomes Measurement Information System (PROMIS) fatigue short form.
3. Neurotoxicity, as measured by the FACT/GOG-Neurotoxicity (Ntx) 4-item subscale.
4. Bother from side effects, as measured by a single-item GP5 "I am bothered by side effects of treatment," rated on a 5-point Likert scale, is part of the FACT-G.
5. Physical function as measured with the PROMIS-physical function scale short form (8c 7-Day).

Justification for PROs in NRG GY018

NRG-GY018 is being proposed as a randomized phase III study examining paclitaxel and carboplatin combination chemotherapy with the checkpoint inhibitor, pembrolizumab (MK-3475) or placebo, in patients with advanced stage or recurrent endometrial cancer. This proposal builds upon GOG-0209, which was a phase III clinical trial comparing the combination regimen of paclitaxel and carboplatin (TC) to TAP. In this trial, investigators demonstrated less toxicity and small HRQoL differences favoring TC, and a non-inferior PFS and OS with the doublet regimen (Miller, 2012). Consequently, with demonstrated non-inferiority to TAP, TC has emerged as the global first-line standard for advanced endometrial cancer.

Moreover, immunotherapy has emerged as a therapeutic strategy in patients with advanced stage or recurrent EC (Vanderstraeten, 2014, Coosemans, 2014), and presents the opportunity to improve response rates and quality of life. However, as noted by Langer (2016), pembrolizumab (MK-3475) with chemotherapy was recently tested on a small cohort of female patients, and in this trial, the most common treatment related adverse event of any grade was fatigue (64% pembrolizumab (MK-3475) + chemotherapy vs 40% chemotherapy alone). While preclinical and clinical observations support the safety and efficacy of checkpoint inhibitors in combination with a cytotoxic chemotherapy backbone (paclitaxel and carboplatin) in patients with advanced stage or recurrent endometrial cancer, it is important to examine the potential HRQoL benefits and risks associated with this new therapeutic strategy within a Phase III trial for advanced or recurrent endometrial cancer patients.

Patient-reported Outcomes Objectives & Hypotheses

Building upon the results from GOG-0209, we will measure PROs in order to determine whether the addition of pembrolizumab (MK-3475)/placebo to standard combination chemotherapy is associated with improved physical function and quality of life due to decreasing disease burden and whether fatigue is significantly worse in the treatment arm containing pembrolizumab (MK-3475). In addition, we will explore whether pembrolizumab (MK-3475) is associated with neurotoxicity since little is known about the effect of pembrolizumab (MK-3475) on peripheral neuropathy when combined with paclitaxel. We

will also explore whether there are overall between-arm differences on patients global self-reported bother from side effects.

We hypothesize that the addition of pembrolizumab (MK-3475) will improve the efficacy of paclitaxel and carboplatin in advanced stage and recurrent endometrial cancer patients with acceptable toxicity and an associated improvement in physical function and quality of life. Therefore the primary QOL question examines whether chemotherapy + pembrolizumab (MK-3475) is associated with improved physical function and quality of life due to its presumably enhanced anti-tumor effect, compared to chemotherapy + placebo. An alternative and additional question is whether the possible increased toxicity of chemotherapy + pembrolizumab (MK-3475) will offset any advantages it may have over the chemotherapy backbone alone in clinical outcome (response rate, time to progression or survival). Further, it is reasonable to explore the extent to which any additional side effects might affect QOL (i.e., if fatigue for example is significantly worse for patients included in the pembrolizumab (MK-3475) arm, how does this affect their overall quality of life?).

Patient Reported Outcomes and Assessment Intervals

The PROs described below represent state-of-the-science HRQoL measurement for endometrial cancer trials, most recently demonstrated through GOG-0249 (M Randall et al, ASTRO 2017 Plenary; V von Gruenigen et al, ASCO 2018). Measures include the FACT-–Endometrial Trial Outcome Index (FACT-En-TOI), the FACT/GOG-Neurotoxicity (Ntx) 4-item Subscale, and a 7-item Patient Reported Outcomes Measurement Information System (PROMIS) fatigue short form.

Quality of Life will be measured by the Functional Assessment of Cancer Therapy – Endometrial Trial Outcome Index (FACT-En-TOI). The FACT Measurement system produces three subscales that are clinically relevant to the physical and functional issues of cancer patients, two of which are general, cutting across all cancers, one that is targeted to endometrial cancer. The FACT-En TOI, comprised of a 7-item Physical Well-being (PWB) scale, a 7-item Functional Well-being (FWB) scale, and a 16-item Endometrial Cancer Subscale (ECS) will be analyzed as the primary comparison between treatment arms. Bother from side effects, as measured by a single-item GP5 “I am bothered by side effects of treatment”, rated on a 5-point Likert scale, is part of the PWB, and will serve as an exploratory endpoint to further understand potential between-arm differences. Physical function will be measured with the 8-item PROMIS-physical function short form (8c 7-Day).

Neurotoxicity will be measured by the FACT/GOG-Neurotoxicity (Ntx) 4-item scale. This is a brief, reliable and valid assessment of pain, numbness and tingling in the extremities, and functional limitations caused by peripheral neuropathy from chemotherapy, and has been shown to be sensitive to treatment arm differences across numerous gynecologic oncology trials (Huang et al, 2007)).

Fatigue will be measured by the 7-item PROMIS-Fatigue Short Form. A recent psychometric validation study conducted in cancer patients indicated that the PROMIS Cancer Fatigue Short Form items loaded on a single factor (CFI = 0.948), and the scale demonstrated good

internal consistency reliability in two cancer patient samples (Cronbach's alphas = 0.86). Correlations with psychosocial measures were significant (p values < .0001) and in the expected direction, offering evidence for convergent and concurrent validity. PROMIS Fatigue scores were significantly higher in patients who met case definition criteria for cancer-related fatigue (p < .0001), demonstrating criterion validity. This provides evidence that the PROMIS Cancer Fatigue Short Form is a reliable and valid measure of fatigue in cancer patients (Cessna et al, 2016). Validation analyses of this measure in the endometrial cancer patient population of GOG-0249 is currently underway, pending publication of the GOG-0249 clinical manuscript.

Assessment Intervals **(14-OCT-2020)**

All pMMR patients will be asked to complete a survey at five time points:

1. Week 0. Baseline/prior to cycle 1. The baseline time point permits a pre-treatment status assessment.
2. Week 6. Cycles 3 and 6 examine active treatment differences, in which disease may be responding and side effects may or may not differ between treatment arms.
3. Week 18. Start of maintenance
4. Week 30. Cycle 9 may indicate the chemotherapy recovery phase since patients are 15 weeks from the last cytotoxic therapy.
5. Week 54. Cycle 13 may represent the median PFS.

Note that even if treatment stops early, assessments are to be completed at the same time the patient would have been scheduled to receive treatment (i.e., baseline, 6 weeks, etc).

If treatment is delayed, conduct the assessment at the time the treatment is scheduled (not the time the treatment is actually given) so that the effect of the treatment on QOL or toxicities is measured. IT IS ACCEPTABLE TO CONDUCT THESE ASSESSMENTS BY TELEPHONE.

PRO Assessments will be completed through Medidata Patient Cloud ePRO (see Section 8.6) at the scheduled times, even for patients who are removed from study treatment. (07/03/2019)

A Coversheet is always required even if assessment cannot be completed, in order to document reasons that the data were not captured. (08-DEC-2020)

12. ASSESSMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [*Eur J Ca* 45:228-247, 2009] Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured

in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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

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

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

NRG will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a

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

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

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases, e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

12.2 Response Criteria (07/03/2019)

Determination of response should take into consideration all target (See 12.2.1) and non-target lesions (See 12.2.2).

12.2.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters (i.e. the nadir) while on study.

12.2.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) Progressive Disease (PD):

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.2.3 Evaluation of Best Overall Response

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

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions		New Lesions*	Time Point Response
CR	CR		No	CR
CR	Non-CR/Non-PD		No	PR
CR	NE		No	PR
PR	Non-PD or NE		No	PR
SD	Non-PD or NE		No	SD
NE	Non-PD		No	NE
PD	Any		Yes or No	PD
Any	PD**		Yes or No	PD
Any	Any		Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

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

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions		New Lesions*	Time Point Response
CR		No	CR
CR		No	Non-CR/non-PD*
Non-CR/non-PD		No	Non-CR/non-PD*
NE		No	NE
Unequivocal PD		Yes or No	PD
Any		Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.2.4 Best Overall Confirmed Response

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of results. Therefore, for GY018, confirmation of response is not required.

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

12.3 Duration of Response

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

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

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

12.4 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first, or date of last contact if neither progression nor death has occurred.

12.5 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

13. DATA AND RECORDS (24-FEB-2023)

13.1 NRG Data Management Forms

Refer to the CTSU member website for the table of Required Forms and Materials.

13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.5.1, 7.5.1.1 and 7.6 for information about expedited and routine reporting.

13.3 Enhanced Centralized Monitoring

13.3.1 Eligibility

The source records which document the eligibility for the first patient enrolled from each site (as identified by a unique NCI identifier) will be reviewed for completeness and consistency with the eligibility criteria, the data reported during the enrollment process and the data reported on the case report forms (CRFs). Sites enrolling rapidly to the trial may undergo monitoring for up to three patients.

For eligibility review, documents are to be submitted within two weeks of patient enrollment by uploading into the Auditing and Monitoring portal on the CTSU website.

The pre-enrollment documents to be reviewed include:

- Signed and dated consent forms will be submitted to review for signatures, date of consent, and patient consent to optional studies.
- Baseline imaging reports to confirm RECIST measurable disease.
- Medical history and physical examinations records and laboratory results, including all blood tests and pregnancy test when appropriate.

- Pathology report, including MMR IHC results, documenting histology of original primary tumor. (Note: institutional (local) MMR IHC results are not required for sites in Japan.) **(08-DEC-2020)**

13.3.2 Drug Accountability, Drug-Dose Compliance, and Adverse Events **(19-MAY-2022)**
The source records and adverse events (AEs) after the first 6 cycles of treatment (all treatment prior to maintenance phase) for the first patient enrolled at each site will be reviewed for compliance with the protocol, completeness and consistency with the data reported on the case report forms, and drug accountability records. The documents listed below are to be uploaded to the Auditing and Monitoring portal on the CTSU website approximately 5 months after study enrollment.

The documents to be reviewed include:

- Study drug orders, treatment dose calculations and administration records.
- Reports from protocol-directed laboratory studies.
- Reports from any additional tests performed to document an adverse event.
- All progress notes relating to pre-therapy history and physical and AE assessments
- Summaries of hospital admissions and discharge for hospitalizations.
- Summaries of surgical procedures performed.

The review of pharmacy drug accountability records will be coordinated by the NRG Oncology monitor. Unblinded pharmacy records MUST NOT be uploaded to the CTSU website. Pharmacy records MUST only be shared by the designated unblinded personnel.

13.4 Enhanced Auditing (21-MAY-2021)

- Additional Cases Audits

  During the audit visits that occur under the CTEP audit procedures, additional cases will be reviewed to ensure that all sites that enrolled patients to the Study will be selected for review.

- Off Cycle Audits for High Accruing Sites

  Any individual site enrolling 5 or more patients will undergo an off-cycle site visit audit, in addition to their regularly scheduled audit, if that site is not due for a regular audit within 1 year of enrolling 5 or more patients.

13.5 Global Reporting/Monitoring (09/24/2019)

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website

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

CDUS-Abbreviated reporting has been assigned to this study; no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via Rave-CTEP-AERS integration.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (07/03/2019) (09/24/2019) (19-MAY-2022) (30-SEP-2022)

This is a study of two populations, making it essentially two clinical trials. One population under study has proficient mismatch repair (pMMR) as determined by a central laboratory. The other population has deficient mismatch repair (dMMR) as determined by a central laboratory. The primary alternative hypothesis for each population is that the addition of pembrolizumab (MK-3475) to the standard of care will prolong the time of progression-free survival (PFS). Patients will be randomized in a 1:1 fashion to treatment arms 1 and 2 after prospectively stratifying them by mismatch repair deficiency (yes versus no), performance status (0 or 1 versus 2), and prior chemotherapy (yes versus no). Block randomization will be used. Accrual will continue with MMR proficient (pMMR) patients until 590 are enrolled or medical judgement intervenes. The dMMR patients will continue to enroll until 220 of this population are accrued. When a population meets its accrual goals, further accrual to that population is to be avoided. Patients can enter according to their local MMR status, but the statistical analyses will be based the central laboratory determined MMR status. Patients who do not have a central MMR status will be excluded.

An interim efficacy analysis will occur after the population (both pMMR and dMMR) completes accrual even if a sufficient number of PFS events are observed beforehand. An O'Brien-Fleming (OBF) type of stopping boundary will be used with a Lan-Demets alpha spending function. The spending function is provided below:

$$\alpha(t) = 2 * \left[1 - \Phi\left(z_{\alpha/2}/\sqrt{t}\right)\right]$$

The total alpha for each population will start at 0.0125 one-sided. It is anticipated that approximately 70% or more of the information will be available at the time of the interim analysis for both populations. The accrual should complete in 29.5 months and 44 months for the pMMR and dMMR patients, respectively. If the interim analysis is conducted with 70% of the information, then the study should have 58% and 50% power to detect the alternative hypotheses for the respective populations (Ha: HR=0.70 for pMMR and Ha: HR=0.60 for dMMR).

If accrual to both populations completes before 50% of the information time (IT) is acquired in either population, then the study will wait until at least 50% IT is obtained in that population before the efficacy interim analysis is conducted. Each population (the dMMR and the pMMR groups) will be evaluated separately and independently. If a population is at least 50% IT when the study closes to both populations, then the efficacy interim analysis for that population will be conducted at that time. In mathematical terms, the approximate timing of the efficacy interim analysis for population k is the maximum of the time when the study

closes to both populations and the time when population k has at least 50% of the planned information for the final analysis.

If the null hypothesis for one group (e.g. dMMR) is rejected before the other group is tested, then all of the alpha (a total of 0.0125) will be forwarded to the other group (e.g. pMMR). The alpha spent on the other group using the OBF function will be adjusted according to the rules outlined by Maurer and Bretz (e.g. see their example on pages 317-8). In the case(s) where both null hypotheses are being tested at the same time (e.g. if both groups had more than 50% at the time of study closure to accrual), the null hypothesis associated with the dMMR population will be tested first, then followed by the pMMR population. If the null hypothesis can be rejected for the dMMR population, then its alpha will be forwarded. Otherwise, the order of testing will be dictated by the timing of data maturation and the alpha forwarded as appropriate.

Patients within the pMMR group will be monitored until 394 have disease progression or die (PFS endpoint) for a final efficacy analysis. The null hypothesis of equal hazard rates (i.e. Ho: HR = 1.0) will be tested with a one-sided log-rank test. If the true hazard ratio is 0.70 (i.e. Ha: HR = 0.70), then the study has at least 90% power of detecting this effect. The data in this group are expected to mature for a final analysis somewhere between 36 months and 41 months after study activation assuming a conservative accrual rate of 20 patients per month.

Patients within the dMMR group will be monitored until 168 PFS events occur. The null hypothesis of equal hazard rates (i.e. Ho: HR = 1.0) will be tested. If the true hazard ratio is 0.60 (i.e. Ha: HR = 0.60), then the study has at least 85% power of detecting this effect. The data in this group are expected to mature somewhere between 55 months and 68 months after study activation assuming a conservative accrual rate of 5 patients per month.

14.2 Study Endpoints

Primary

1. Progression-free survival (PFS)

Secondary

1. Adverse events as assessed by CTCAE.
2. Objective tumor response as assessed by RECIST 1.1.
3. Duration of objective response (the time difference between the dates of first response and first progression; patients who do not progress are considered censored).
4. Overall Survival (OS).
5. Quality of life (QOL) and patient-reported outcomes (PROs), measured by the FACT-En-TOI, the FACT/GOG-Ntx subscale (short), PROMIS-Fatigue (short form), the PROMIS-physical function (short form) and a single-item measuring bother from side effects of cancer therapy.
6. Pembrolizumab (MK-3475) treatment and self-reported neurotoxicity with FACT/GOG-

Ntx.

7. Concordance between institutional MMR IHC testing and centralized MMR IHC.
8. The effect of pembrolizumab (MK-3475) on PFS and OS by PD-L1 IHC (combined positive score (CPS)) within pMMR and dMMR populations.
9. Measures of association between PD-L1 IHC (CPS) and MMR status.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

1. The null hypotheses are that the hazard ratios of experimental to control regimens are equal to 1 versus the alternative hypotheses that the hazard ratios are less than 1 (i.e. $H_0: HR \geq 1$ versus $H_1: HR < 1$). The endpoint for these hypotheses is PFS.

14.3.2 How Primary Endpoints Will Be Analyzed

1. The primary hypotheses will be tested with a stratified log-rank statistic. The distribution of these statistics will be approximately normally distributed, and this assumption will be used to draw inferences about regimen activity.

14.3.3 Sample Size and Power Calculations: **(19-MAY-2022)**

A first approximation to the number of events required in order to have a study with probability of type I error (α) and power ($1 - \beta$) is given by Schoenfeld's equation:

$$D = \frac{4\left(Z_{\alpha} + Z_{1-\beta}\right)^2}{(ln\{HR\})^2}$$

The values of alpha are 0.0125 for each population. If one analysis rejects the null hypothesis, alpha will be forwarded to the other population so that it can be tested at a higher level of significance. The value of beta is 10% (power = 1 – 0.10 = 0.90 or 90%) for the pMMR population when testing at the 0.0125 level. For the dMMR population, beta is 15% when testing at the 0.0125 level.

Based on historical data within NRG Oncology (studies not published), we have the following models for PFS and OS:

$$S_p(t) = 0.90exp(-0.07\ t) + 0.10$$

$$S_s(t) = 0.90exp(-0.03244\ t) + 0.10$$

The data indicate that the population under consideration has about 10% who do not progress or die for a long time. Using these models, the expected median PFS time is about 11.6 months whereas the median OS is about 25 months in the reference arm. If the investigative regimen reduces the hazard of PFS by 0.70 relative to the reference regimen (proportional hazards), then the median PFS is delayed to 17 months (a 5.4 month delay). Likewise, if the investigative regimen reduces the hazard of death by 0.7 (proportional hazards), then the median OS is delayed to 36.9 months (11.9 months or almost a full year). This effect would

be considered by many investigators to be a substantial impact on OS. However, a 30% reduction in the hazard rate is somewhat small so fairly large samples are necessary to detect it.

Using Schoenfeld's equation with the PFS parameters, we obtain $Z_\alpha = 2.241$, $Z_{1-\beta} = 1.282$, and $D = 392$ at a HR=0.70. To assure that the observation of 392 PFS events occurs in a reasonable timeframe, we plan on accruing 590 patients. Likewise for the dMMR patients, $Z_\alpha = 2.241$, $Z_{1-\beta} = 1.036$, and $D = 168$ at a HR=0.60. To assure that the observation of 168 PFS events occurs in a reasonable timeframe, we plan on accruing 220 patients.

A plot of the reference regimen's anticipated survival functions are provided below:

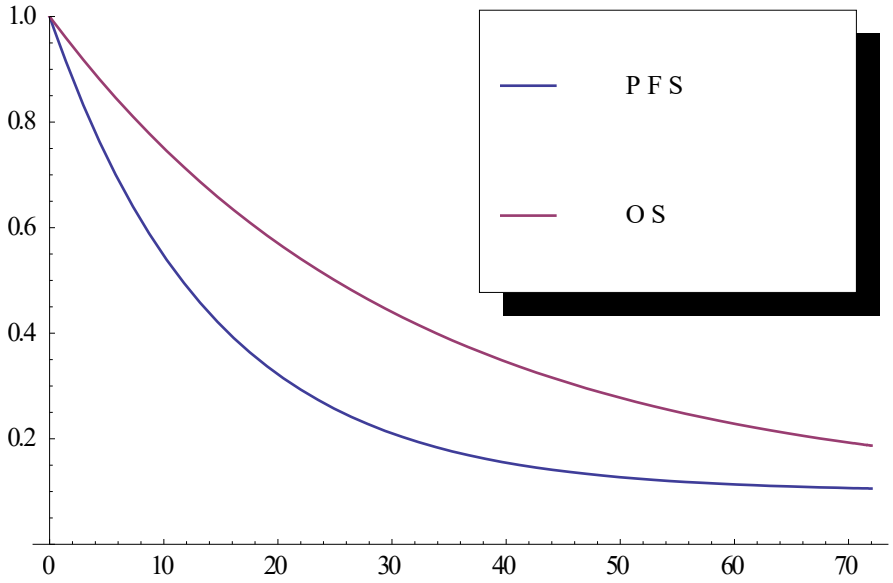


Figure: Progression-free survival (PFS) and overall survival (OS) functions against months of study entry.

As indicated by the graph, almost 20% of the patients survive beyond 6 years. The proportion of long term progression-free survival patients is 10% in the reference regimen. If a proportional hazards assumption is assumed, then we expect $0.10^{0.70} = 0.20$ or 20% to survive progression-free for a long time when the HR is 0.70. Additionally, if the HR = 0.60, then we expect 25% of the patients to survive progression-free long term. If the experimental regimen does not produce this effect, the proportional hazards assumption will be violated. If the survival function for the experimental arm approaches the survival function for the reference regimen in the long term, the estimated hazard ratio is a function of follow-up time. Often the test becomes less significant the longer the investigators wait to conduct an analysis.

An O'Brien-Fleming type of stopping boundary will be used with a Lan-Demets alpha spending function for a single efficacy interim analysis in each population (both pMMR and

dMMR). The interim analysis necessitates a slight boost to the total number of events for the pMMR group, which is 394. The dMMR group requires roughly the same number of PFS events relative to the Schoenfeld estimate (i.e. 168 PFS events). **(07/03/2019) (09/24/2019)**

14.4 Study Monitoring of Primary Objectives (09/24/2019) (19-MAY-2022) (30-SEP-2022)

(Interim Analysis)

An interim futility analysis is planned for the pMMR group. At 50% information time (i.e. at approximately 196 PFS events), a Wieand type futility rule will be applied. That is, if the log-rank test statistic (experimental to reference) before squaring is greater than zero indicating a higher risk of eventing on the experimental arm, then the study will consider early termination for this population. If the null hypothesis is true, then the study has a 50% probability of early termination. The chance of this event is rare under the alternative hypothesis (e.g. $1 - \Phi\left(-\sqrt{D} \cdot ln\{HR\}/2\right)$) which is 0.0063 when the HR = 0.70. See Wieand et al. for further discussion. The timing of the interim futility analysis is expected to occur sometime between 22 and 24 months after activation.

An interim futility analysis is also planned for the dMMR group. At 50% information time which is after 84 PFS events, a separate Wieand type futility rule will be applied. As before, if the log-rank test statistic (experimental to reference) before squaring is greater than zero indicating a higher risk of eventing on the experimental arm, then the study will consider early termination for this population. If the null hypothesis is true, then the study has a 50% probability of early termination. The chances of early termination are small when the HR = 0.60 (about 0.01). The impact of the interim analysis on final power is minimal even when the HR=0.70. The timing of the interim analysis is expected to occur sometime between 32 and 35 months after activation.

An interim efficacy analysis will occur after the population (both pMMR and dMMR) completes accrual even if a sufficient number of PFS events are observed beforehand. A "sufficient number" is defined as 50% information time. An O'Brien-Fleming type of stopping boundary will be used with a Lan-Demets alpha spending function. The spending function is provided below:

$$\alpha(t) = 2 * \left[1 - \Phi\left(z_{\alpha/2}/\sqrt{t}\right)\right]$$

The total alpha for each population will start at 0.0125. It is anticipated that approximately 70% or more of the information will be available at the time of the interim analysis for both populations. The accrual should complete in 29.5 months and 44 months for the pMMR and dMMR patients, respectively. If the interim analysis is conducted with 70% of the information, then the study will spend about 0.003 alpha (Z=2.765) and should have 58% and 50% power to detect the alternative hypotheses for the respective populations (Ha: HR=0.70 for pMMR and Ha: HR=0.60 for dMMR).

If accrual to both populations completes before 50% of the information time (IT) is acquired in either population, then the study will wait until at least 50% IT is obtained in that population before the efficacy interim analysis is conducted. Each population (the dMMR

and the pMMR groups) will be evaluated separately and independently. If a population is at least 50% IT when the study closes to both populations, then the efficacy interim analysis for that population will be conducted at that time. In mathematical terms, the approximate timing of the efficacy interim analysis for population k is the maximum of the time when the study closes to both populations and the time when population k has at least 50% of the planned information for the final analysis.

If the null hypothesis for one group is rejected before the other group is tested, then all of the alpha (a total of 0.0125) will be forwarded to the other group. The alpha spent on the other group using the OBF function will be adjusted according to the rules outlined by Maurer and Bretz (e.g. see their example on pages 317-8). In the case(s) where both null hypotheses are being tested at the same time (e.g. if both groups had more than 50% at the time of study closure to accrual), the null hypothesis associated with the dMMR population will be tested first, then followed by the pMMR population. If the null hypothesis can be rejected for the dMMR population, then its alpha will be forwarded. Otherwise, the order of testing will be dictated by the timing of data maturation and the alpha forwarded as appropriate.

In each group, at the time of the final PFS analysis (significant interim or final analysis), an interim OS futility analysis will be performed and the (OS interim analysis) results released along with the PFS results, at that time. The null hypothesis of Ho: HR = 1.0 will be tested against the one-sided alternative Ha: HR > 1.0 at the 10% level of significance. Rejection of Ho would be indicative of a concern for worse OS in the experimental arm. We anticipate about 250 deaths in the pMMR group and 115 deaths in the dMMR group at their respective final PFS analysis. The final OS analysis will be performed when about 364 (150) OS events are observed in pMMR (dMMR) group, respectively. This corresponds to about 60 and 86 months after trial activation in the pMMR and dMMR groups respectively.

Interim Monitoring by the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

Compliance with follow-up and patients lost to follow-up during the maintenance phase after unblinding will be carefully monitored by the NRG Oncology Data Monitoring Committee. **(14-OCT-2020) (21-MAY-2021)**

14.5 Accrual/Study Duration Considerations

The maximal accrual rate for GOG 286B was about 25 patients per month. We believe this accrual can be attained on this study and may accrue at a higher rate due to expanded eligibility and increased participation in other countries. The accrual goal is 590 patients with proficient MMR tumors and 220 patients with deficient MMR tumors. The period of active accrual to the pMMR group is expected to be 29.5 months. The period of active accrual to the dMMR is expected to be about 44 months.

14.6 Secondary or Exploratory Endpoints (including correlative science aims) (07/03/2019) (09-MAR-2022)

These tests will be 1-sided. The power of a test of the null hypothesis of equal hazards across both treatments can be approximated with:

$$Power = \Phi\left[-\frac{\theta\sqrt{D}}{2} - 1.645\right]$$

where D is the number of events/deaths and $\theta = ln(HR)$.

Toxicities will be screened for differences between treatments by using an exact method or a Chi-Sq test. For a given adverse event, each patient will be graded according to the worse grade experienced while on therapy (and within 30 days of treatment). These toxicities will then be divided into two or three categories such as mild, moderate, and severe or mild to moderate versus severe. The rates of severe toxicities may be characterized by risk ratios or odds ratios with confidence intervals (unadjusted for multiplicity). The number of toxicities examined is usually fairly large, so these analyses will be considered exploratory and may be inspected in light of other studies.

Historical data on GOG 286B indicate that between 50 and 70% of patients were evaluable for response. That translates to about 300 to 400 pMMR patients with measurable disease on this study. The probability of response on the reference regimen should be about 20%. The power of the study to detect an increase in the probability of response by 15% should be at least 88% (e.g. Ho: p1 = p2 = 0.20 versus Ha: p1 + 0.15 <= p2; n1 = n2 = 150). This test can be carried out with a Fisher's Exact Test. The duration of response will be characterized and compared by treatment with KM curves. No formal testing will be done.

The patient's MMR IHC status will be assessed for prognostic value by conducting stratified log-rank tests or Cox Proportional Hazards (PH) modeling when assessing the impact on PFS or OS. When assessing the impact on the probability of response, a logistic regression model will be considered and include other pertinent variables that may influence response.

Assessing the predictive value of MMR IHC status for regimen efficacy is generally considered more challenging due to low statistical power even in large sample sizes such as the one given by this study. The lack of balance between MMR proficient and dMMR makes the success of this study less likely (if there is one actually present). A Cox PH model will be used to assess this effect through an interaction term. A similar type of analysis may be attempted with response using logistic regression.

The concordance of institutional MMR IHC testing and centralized MMR IHC will be characterized by agreement statistics such as kappa statistics (e.g. Cohen's kappa coefficient).

The effectiveness of pembrolizumab (MK-3475) will be compared by PD-L1 status (CPS). A

formal test will be conducted by examining the interaction term between pembrolizumab (MK-3475) treatment (yes or no) with PD-L1 status. Since these tests often have poor power, descriptive examinations of the HR for pembrolizumab (MK-3475) treatment can be provided in subset analyses by PD-L1 CPS assessment. If the association between PD-L1 status is highly associated with MMR IHC status, it may not be possible to do separate analyses within the MMR IHC groups. In this case, the analyses will be conducted by pooling the MMR IHC groups together.

The association between PD-L1 CPS status and MMR IHC status will be assessed with odds ratios. A test may be conducted with a Fisher's Exact Test, and confidence intervals will be provided.

14.6.1 Secondary Hypotheses and Endpoints: The expected level of detail for secondary hypotheses will be less than for the primary hypothesis and endpoint.

The secondary endpoints are listed in section 14.2. The null hypothesis for secondary objective 1 is that the probability of having a severe toxicity in the treatment regimen is the same as in the reference regimen. The null hypothesis for secondary objective 2 is that the probability of response in the treatment regimen is the same as in the reference regimen. The null hypothesis for secondary objective 4 is that OS is the same by MMR IHC status. Another null hypothesis for this objective is that MMR IHC status does not interact with treatment to produce a differential impact on OS. In this case, MMR IHC status may be prognostic but still not predictive. The null hypothesis for objective 8 is that the hazard ratio for pembrolizumab (MK-3475) treatment to placebo treatment is the same irrespective of PD-L1 CPS (<1 and ≥ 1). This hypothesis may be evaluated separately within the pMMR and dMMR groups if there is a sufficient number of PD-L1 groups in each subset. If the association between PD-L1 and MMR IHC status is very high, then MMR IHC status may be ignored. The null hypothesis for objective 9 is that the odds ratio of PD-L1 and MMR IHC status is 1.0.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

See sections 14.2 and 14.6.

14.6.3 Interim Analysis for All Other Endpoints

See section 14.4.

14.6.4 Power Calculations: power can be provided as applicable for selected secondary endpoints, if any. The power is based on the sample size for the primary endpoints.

See section 14.6.

14.6.5 Expected Sample Size or Patient Cohorts:

See sections 14.3.3 and 14.5.

14.6.6 Patient reported outcome (PROs) **(08-DEC-2020)**

The QOL/PRO hypotheses are to assess whether the patient-reported quality of life (QoL), physical function, and fatigue are different when adding pembrolizumab (MK-3475) to chemotherapy (carboplatin + paclitaxel) during treatment and maintenance period. Due to the lack of sufficient statistical power in the dMMR group, the analysis for QOL/PRO will be conducted only in the pMMR patient population.

The QOL/PRO endpoints are the patient-reported QoL as measured with the FACT-En TOI, physical function as measured with the PROMIS-physical function short form, fatigue as measured with the PROMIS-Fatigue (short form), and neurotoxicity symptoms as measured with the FACT/GOG-Ntx subscale (short). Items in the FACT-En TOI and the FACT/GOG-Ntx subscale (short) are scored using a 5-point scale (0 = not at all; 1=a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). According to the FACIT measurement system, a subscale score was the summation of the individual item scores if more than 50% of subscale items were answered. Negative statements (or questions) were reversed prior to score calculation. When unanswered items existed, a subscale score was prorated by multiplying the mean of the answered item scores by the number of items in the subscale. A total FACT-En TOI score is the sum of the subscale scores if more than 80% of the FACT-En TOI items provide valid answers. The items in the PROMIS-Fatigue short form are rated on a five-point scale (1=never; 2=rarely; 3=sometimes; 4=often; 5=always). A PROMIS Fatigue score and a PROMIS physical function score are calculated by summating the item scores. In case some items are not answered or the answers are invalid, a PROMIS-Fatigue score will be imputed using the same method described in FACIT measurement system. A PROMIS-Fatigue score and a PROMIS physical function score ranges from 7 to 35 and from 8-40 respectively, which both can be converted to the PROMIS Scale scores.

The QOL/PRO endpoints will be compared at 6 weeks (pre-cycle 3), 18 weeks (pre-cycle 6), 30 weeks (pre-cycle 9), and 54 weeks (pre-cycle 13) post the starting of protocol chemotherapy. However, death, illness, noncompliance, and missed appointment can cause missing information that increases over time. A patient is considered evaluable for QOL/PRO analysis if she provides valid baseline and at least one follow-up QOL/PRO assessments. At least 80% evaluable patients are expected for the QOL/PRO analysis.

A linear mixed model for repeated measures will be used to estimate and compare the mean differences between the treatment groups. Model covariates will include the patients' randomly assigned study treatment, age at enrollment onto the study, pre-treatment QOL/PRO score, assessment time and treatment-by-time interaction. The stratification factors will be the same factors included in the clinical primary analysis. Hochberg's step-up multiple testing procedure (Hochberg, 1988) will be used to adjust p-values for each assessment time points estimated from the fitted model.

QOL/PRO will not be used for labeling purposes. They will be considered as supplemental information. Therefore the QOL/PRO will be tested at a significant level of 5% (two-sided). To control the overall type I error for the multiple QOL/PRO endpoints (the FACT-En TOI, PROMIS-Physical function, and the PROMIS-Fatigue short form), each of the QOL/PRO endpoints will be tested at a significant level of 1.67% (two-sided).

Exploratory analyses will be conducted to explore whether pembrolizumab (MK-3475) is associated with patient-reported neurotoxicity symptoms and whether patients are bothered more from side effects when adding pembrolizumab (MK-3475) to chemotherapy and will be examined at significant level of 5% respectively.
Missing PRO information
Patient death, noncompliance, missed clinic appointments, and patient illiteracy can cause observations to be missed. One or more of the PRO assessments may be missing for an individual on any occasion. Missing information is troublesome particularly in studies involving repeated patient assessments. The frequency that assessments are missed will be monitored every 6 months throughout the study. Study Coordinators will be working with the Study Team and the NRG's Patient Centered Outcomes Research Committee to identify reasons that data are missing and recommending remedial actions when possible.

The PRO instruments used in this study have been translated to different languages (Spanish, French). Women who are unable to read or have difficulty reading, will not be required to participate in the PRO component of this study, however, a woman may elect to have the items read to her and be assisted in completing the instruments.

14.7 Exploratory Hypothesis and Endpoints (07/03/2019)

Exploratory Hypotheses and endpoints are discussed in sections 14.2 and 14.6.1.

14.8 Gender/Ethnicity/Race Distribution (21-MAY-2021)

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	6		0		6
Asian	17		0		17
Native Hawaiian or Other Pacific Islander	1		0		1
Black or African American	78		0		78
White	452		23		475
More Than One Race	12		4		16
Total	566	0	27	0	593

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	5		0		5
Asian	145		0		145
Native Hawaiian or Other Pacific Islander	0		0		0
Black or African American	0		0		0
White	67		0		67
More Than One Race	0		0		0
Total	217		0		217

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APPENDIX I - CARCINOMA OF THE ENDOMETRIUM FIGO CLASSIFICATION 2009

Stage I*	Tumor confined to the corpus uteri.
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae[#]
IIIB*	Vaginal and/or parametrial involvement[#]
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes[#]
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

*Either G1, G2, or G3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[#]Positive cytology has to be reported separately without changing the stage.

APPENDIX II – PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX III- CARBOPLATIN DOSE CALCULATION INSTRUCTIONS (09/24/2019) (07-FEB-2020) (21-MAY-2021)

1) The Cockcroft-Gault formula will be used in NRG Oncology trials.

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using creatinine clearance (mL/min) from the Cockcroft-Gault formula.

2) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dL.**

3) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

4) Carboplatin doses are recommended to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

5) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR [or estimated CrCl] + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x actual body Weight* (kg)}}{\textbf{72 x serum creatinine (mg/dl)}} \quad \textbf{\{x 0.85 } \textit{\textbf{if female}}\textbf{\}}$$

Notes:
1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient.
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
   c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**

d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) (+ 45.5 females) or (+ 50 for men)
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

At the time of a dose modification for toxicity:
If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

- For cycle lengths greater than or equal to 21 days, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without being considered a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21-day or greater cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

- Chemotherapy doses are recommended to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

APPENDIX V - CTEP COLLABORATIVE AGREEMENTS LANGUAGE

The agent supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as

described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   E-mail: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX VI - TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES (21-MAY-2021) (09-MAR-2022)

I. Obtaining a Bank ID for Translational Science Biospecimens

One Bank ID (N # # # # # # # # #) is assigned per patient per study. All translational science biospecimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component.

Please contact User Support if you need assistance (support@nrgoncology.org).

II. Requesting Translational Science Biospecimen Kits

One single chamber kit will be provided per patient for the collection and shipment of frozen whole blood; however, whole blood from more than one patient may be shipped together in one kit.

Sites can order kits online via the Kit Management link (https://kits.bpc-apps.nchri.org/). Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the NRG BB-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

Note: Unused materials and kits should be returned to the NRG BB-Columbus. A pre-paid shipping label for the return of unused supplies and kits may be obtained via the Kit Management system. Select "Empty Kit" for package contents when returning unused kits.

Sites in Korea and Japan: Translational science biospecimen kits are not provided by the NRG BB-Columbus for sites in Korea and Japan.

III. FFPE Tissue Shipped to the NRG BB-Columbus

- Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (e.g., primary, metastatic, recurrent, persistent).
    - Archival **primary (FP01)** and **metastatic (FM01)** tumor should be collected prior to the patient receiving any treatment.
    - **Recurrent** and **persistent** tumor should be collected prior to the patient receiving any study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled **recurrent primary (FRP01)** or **persistent primary (FPP01)**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic (FRM01)** or **persistent metastatic (FPM01)**, respectively.
    - **Primary neoadjuvant (FPT01)** and **metastatic neoadjuvant (FMT01)** tumor should be

collected after the patient receives neoadjuvant treatment. Neoadjuvant tumor should only be submitted if tumor collected prior to receiving any treatment (FP01 or FM01) is not available.

- Only one block may be submitted per tissue type.

- All FFPE tissue should be submitted with the corresponding pathology report, a completed copy of the FFPE Materials Verification Form (Appendix X), and an electronically-completed copy of Form TR.
  - **Sites in Korea and Japan** must provide an English translated copy of the corresponding pathology report. Note: The entire report must be translated, typed, and include diagnosis, clinical history, gross description or block number, and microscopic findings.

FFPE Biospecimen Requirement
Every attempt should be made to provide a block on a permanent basis; however, if a block cannot be provided on a permanent basis, then 10 unstained slides (charged, 5µm) should be submitted. All tissue sections should be cut sequentially from the same block.

Labeling FFPE Tissue
A waterproof permanent marker or printed label should be used to label each translational science tissue biospecimen with:

REQUIRED FFPE BIOSPECIMEN LABELING
Bank ID (N # # # # # # # # #)*
NRG ID (X X # # # -GY018- # # # # #)
Biospecimen Code (see section 10)
Collection Date (mm/dd/yyyy)
Surgical Pathology Accession Number
Block Number

***** *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.*

Failure to label biospecimens with all data fields shown in the sample label above may result in delayed processing and/or inability to utilize biospecimens.

IV. Whole Blood Shipped to the NRG BB-Columbus
1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount. **Do <u>not</u> use glass blood collection tubes.**
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Immediately freeze the whole blood in an upright position in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection. **Sites in Korea and Japan** should ship to the respective central lab within 5 weeks of patient registration.

Labeling Whole Blood

A waterproof permanent marker or printed label should be used to label each translational science whole blood biospecimen with:

REQUIRED WHOLE BLOOD BIOSPECIMEN LABELING
Bank ID (N # # # # # # # # #)*
NRG ID (X X # # # -GY018- # # # # #)
Biospecimen Code (WB##)
Collection Date (mm/dd/yyyy)

** Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.*

Failure to label biospecimens with all data fields shown in the sample label above may result in delayed processing and/or inability to utilize biospecimens.

V. Submitting Form TR

A specimen transmittal form (i.e., Form TR) for each biospecimen will be available in the **Translational Research Folder in Rave**, once the Specimen Consent (located in the Baseline Folder) has been completed.

An electronically (i.e., Rave) completed copy of Form TR must accompany each biospecimen shipped to the NRG BB-Columbus. **Handwritten forms will not be accepted.**

Note: A copy does not need to be sent to the NRG BB-Columbus if biospecimens are not collected.

Form TR **must** be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a single page PDF. Do not use the "Printable Version" or "View PDF" links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@nrgoncology.org).

VI. Shipping Translational Science Biospecimens

Translational science biospecimens should not be shipped until after patient registration and Bank ID assignment.

An electronically completed copy of Form TR must be included for each translational science biospecimen.

All translational science biospecimens should be shipped to:

NRG BB-Columbus / Protocol NRG-GY018
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205

Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

Sites in Korea and Japan should ship to the respective central lab. The central lab will batch ship all biospecimens to the US.

A. FFPE Tissue Shipped to the NRG BB-Columbus
FFPE tissue, a copy of the corresponding pathology report, and a completed copy of the FFPE Materials Verification Form (Appendix X) should be shipped using your own container at your own expense to the NRG BB-Columbus at the address above.

Do not ship FFPE tissue for Saturday delivery.

B. Whole Blood Shipped to the NRG BB-Columbus
Frozen whole blood should be shipped using the biospecimen kit provided to the NRG BB-Columbus (address above).

Frozen biospecimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen biospecimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen biospecimens.

Frozen biospecimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice) until the biospecimens can be shipped.

Shipping Frozen Translational Science Biospecimens in a Single Chamber Kit
1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen whole blood in a zip-lock bag. If whole blood from more than one patient is included in the same shipment, then place the whole blood from each patient in a separate zip-lock bag.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form TR for each biospecimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management link ((https:/kits.bpc-apps.nchri.org/). Attach the air bill.
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

VII. Banking Translational Science Biospecimens for Future Research (09-MAR-2022)
Biospecimens will remain in the NRG BB-Columbus and made available for approved research projects if the patient has provided permission for the use of their biospecimens for future health research.

Note: Biomarker testing of banked biospecimens will not occur until an amendment to this treatment protocol or separate correlative science protocol is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via the Specimen Consent form. At the time of biospecimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of their biospecimens at any time if the patient changes their mind.

If the patient revokes permission to use their biospecimens, the NRG BB-Columbus will destroy or return any remaining biospecimens. The patient's biospecimens will not be used for any <u>further</u> research; however, any biospecimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with their biospecimens distributed prior to revoking consent.

Note: If return of biospecimens is requested, shipping will be at the site's expense.

APPENDIX VII: DIAGNOSTIC IMAGE COLLECTION SUMMARY (07/03/2019) (14-OCT-2020) (09-MAR-2022) (24-FEB-2023)

Approximate scan collection per subject:

a. ~5 scans per year up to 9 months or until progression
b. After 9 months: ~4 scans per year until progression

1. CT scan or MRI performed once every 9 weeks (+/- 7 days), and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression.
2. If a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 9 weeks (+/- 7 days) for the first 9 months, then every 12 weeks (+/- 14 days) thereafter until progression. See Sections 4.2/4.3.

TRIAD Digital Image Submission:

Transfer of Images Data (TRIAD) is the American College of Radiology (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates images as they are transferred.

TRIAD will be the sole means of image transfer to the IROC Philadelphia DI. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

TRIAD Access Requirements:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section (Section 8.1) for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email: TRIAD-Support@acr.org or 1-703-390-9858.

APPENDIX VIII –CENTRALIZED MMR IHC TESTING LABORATORY MANUAL (07-FEB-2020) (21-MAY-2021) (09-MAR-2022) (19-MAY-2022)

1. BIOSPECIMEN COLLECTION TABLE

Sample	**Archival Formalin-Fixed, Paraffin-Embedded (FFPE) Tumor Tissue (slides)**
Time points	Screening
# samples per time point	12 unstained slides (each 4 micron in thickness) from FFPE block
Label	**Each slide must be labeled with two identifiers**. Label each slide with the NRG Patient ID and Block ID (i.e., Surgical Pathology number and block number). Serially number slides in the order they were sectioned with indelible ink. **The same two identifiers must also be included on the Tissue Sample Transmittal Form.**
Process	Archival tissue samples should be submitted as freshly cut slides. **Slides must be sent within 48 hours of sectioning to NeoGenomics Laboratories, Inc.** **Sections must be prepared using the Superfrost slides provided by PPD.** Place slides in the plastic slide holder provided; put foam pad on top of slides. Tape shut and wrap plastic slide holder with bubble wrap. Place bubble wrapped slide holder in biohazard bag. Package slides with 2-3 cold packs and ship to NeoGenomics Laboratories, Inc., with Tissue Sample Transmittal Form for NRG-GY018/MK3475-868.
Storage condition	Refrigerated (2-8ºC), in dark
Shipping Definitions	The addition of cold/ice/gel packs or as otherwise instructed by PPD Laboratory Manual (Appendix XI), without requirements for temperature monitoring.
Shipping condition	Refrigerated, in dark
Ship to	**NeoGenomics Laboratories, Inc.**
Courier	Refer to PPD Laboratory Manual (Appendix XI) for details

2. RATIONALE FOR COLLECTION

The collection of archival tumor sectioned slides is for the purpose of MMR and PD-L1 IHC biomarker analysis. Submission of required slides for MMR and PD-L1 IHC simultaneously allows for more efficient utilization and processing of tissue samples on trial.

3. GENERAL OVERVIEW AND RECOMMENDATIONS

3.1 SAMPLE REQUIREMENTS

- Tumor tissue for biomarker analysis from an archival tissue sample of a tumor lesion not previously irradiated must be provided in the form of 12 unstained slides freshly cut from an FFPE tissue block. Sections **must** be prepared using the Superfrost slides provided by PPD.
- **A fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow, cytologic specimen, decalcified or formalin fixed sample that was frozen at any point will not be acceptable for analysis. PLEASE NOTE: Decalcification of the sample cannot occur during any part of the tissue processing/embedding/section cutting (surface decalcification) process.**
- Samples identified as "non-decalcified soft tissue from bone" will be accepted and processed ***IF*** the following criteria are met:
  - Confirmation by site, (via the Tissue Sample Transmittal Form), that decalcification was not performed on this sample.
  - Samples must be obtained using standard biopsy techniques normally employed for solid organs or soft tissues. Examples of such techniques include excisional or wedge biopsies obtained with a scalpel, core needle biopsies obtained with modest pressure in a single motion, or snare biopsies.
  - Conversely, an example of an unacceptable bone specimen is a needle biopsy that requires excessive pressure and/or a back-and-forth motion (i.e., bone marrow biopsy technique).
- **Any sample containing bone, irrespective of decalcification status, has a high possibility and risk to be not evaluable due to the following reasons:**
  - Laboratory is unable to section the sample
  - Small bone particles destroy the tissue architecture upon sectioning
  - IHC assay potentially impacted due to bone in the sample
- When completing the **Tissue Sample Transmittal Form (for a soft-tissue from bone sample)**, please ensure the "Anatomic Location of Tumor Tissue Collection" section is completed as follows: "Other" box should be checked and a note entered that the sample is "non-decalcified soft tissue from bone."
  - Please note, omission of these steps will trigger a query to your site to send a local pathology report, which will result in processing delay. If a pathology report is requested, any necessary translations required will result in further processing delays.
- The provided sample should contain tumor specimen sufficient for pathology review and analysis of tumor sample:
  - A minimum of 100 viable tumor cells is required for PD-L1 and MMR immunohistochemical analysis or sample will be reported as not evaluable. If possible, greater than 50% tumor content is preferred if available.

3.2 SUBMISSION OF UNSTAINED SECTIONED SLIDES FROM FFPE BLOCKS

3.2.1 Materials Required For Sample Collection and Shipment

Provided by the Institution:
- Formalin-Fixed, Paraffin-Embedded (FFPE) tissue block
- Sectioning equipment

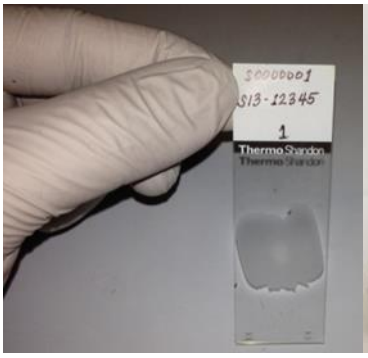
Provided to the Institution:
The following supplies and materials will be provided by PPD. Please see the PPD Manual

(Appendix XI) for details on ordering supplies and materials.

- Slide holder (can accommodate up to 25 slides)
- Positively charged **Superfrost** microscope slides
  - **Please use only the positively charged Superfrost slides provided by PPD** which are standard sized, positively charged microscope slides (75mm x 25mm x 1mm). Other sizes of slides cannot be accommodated.
- Poly foam pouch
- Tissue Sample Transmittal Form for NRG-GY018/MK3475-868
- Biohazard bag
- Shipping container

3.2.2 Sample Preparation and Collection Procedures

1. Sites must freshly cut sections and send out to NeoGenomics Laboratories, Inc., **within 48 hours from sectioning** in order for samples to be received within 2 to 3 days (dependent upon length of shipping) of site slide cutting date. The date slides are cut by the site must be recorded on the tissue sample requisition form.
2. **Use the positively charged Superfrost slides provided by PPD when preparing the unstained slides.**
   a. Standard sized positively charged slides are required for samples; slide measurements are 75mm x 25mm x 1mm.
   b. Other sized slides cannot be accommodated for testing.
   c. Slides should be cut at 4um thickness (4um preferred, 4-5um acceptable) .
3. Ensure the sample has the institutional block ID clearly marked on the outside of the tissue block for identification prior to sectioning.
4. Obtain the 25 slide holder from the PPD bulk supply provided to your site. Each slide holder can hold a maximum of 25 slides.
5. Twelve (12) unstained slides are required to be submitted.
6. **Each slide must be labeled with two identifiers.** Label each slide with the NRG Patient ID and Block ID (i.e., Surgical Pathology number and block number). Serially number slides in the order they were sectioned with indelible ink.
7. Label the 25-slide plastic slide holder.
8. Prepare freshly cut serial sections at 4 micron thickness onto the positively charged microscope slides provide by PPD as close to the day of shipping as possible. Plan to ship cut slides right after sectioning (within 48 hours) to ensure cut slides are received within 2-5 days, dependent upon shipping time, of cutting slides at NeoGenomics Laboratories, Inc.
9. The date slides are cut by the site must be recorded on the Tissue Sample Transmittal Form along with other required information.
10. Number the slides sequentially (serially). Only one section should be on a slide.
11. Standard sized positively charged slides are required for samples; slide measurements are 75mm x 25mm x 1mm. Please use the slides provided by PPD. Other sized slides cannot be accommodated.
12. DO NOT BAKE SLIDES – Only air dry (12 – 24 hours) at room temperature prior to shipment.
13. Place slides in slots of the plastic slide holder in order of sectioning, with a maximum of 25 slides per plastic slide holder. Utilize multiple slide holders as needed.



14. Store in the dark at 2-8ºC until ready to ship.
15. Place foam pad on top of slides, tape shut, and place in poly foam pouch and place in biohazard bag.
16. Using the appropriate PPD-provided shipper, ship cold (2-8ºC) in the dark as specified by the PPD Laboratory Manual (Appendix XI). Sectioned slides should be shipped refrigerated year round.
17. Place a copy of the local pathology report in the shipping container along with the specimen collection bag. Ensure all subject information has been appropriately redacted.
18. Samples should be shipped to NeoGenomics Laboratories, Inc., on the days listed below to ensure arrival to the testing lab prior to the weekend:
    - Mondays through Thursdays
19. Complete the Tissue Sample Transmittal Form for NRG-GY018/MK3475-868 in Rave and print to include with the specimen when packaging for shipment. Make a copy to retain at the site for your records.
    - **The same two identifiers included on each slide must also be included on the Tissue Sample Transmittal Form.**
    - **Failure to include both identifiers on each slide and the Tissue Sample Transmittal Form will result in testing delays.**
20. Using the appropriate PPD-provided shipper, ship cut slides overnight at 2-8C in the dark, along with a copy of the Tissue Sample Transmittal Form for NRG-GY018/MK3475-868, to NeoGenomics Laboratories, Inc., at the address below:

    NeoGenomics Laboratories, Inc.
    31 Columbia
    Aliso Viejo, CA 92656
    Email: pharma_project_support_team@neogenomics.com

21. PPD will provide airway bills for shipping directly to NeoGenomics Laboratories, Inc. Refer to PPD Laboratory Manual (Appendix XI) and other PPD materials for additional shipping instructions and requisition forms.

APPENDIX IX - NRG-GY018 PHARMACY AGREEMENT (07/03/2019) (09/24/2019) (07-FEB-2020) (09-MAR-2022) (24-FEB-2023)

On February 6, 2023, all patient treatment assignments were unblinded. Submission and maintenance of a Pharmacy Agreement for unblinded site personnel is no longer required. A new DTL (without the Unblinded Study Personnel task) is available on the CTSU website and must be completed and signed by the site CI.

The NCI Pharmaceutical Management Branch is usually responsible for blinding patient-specific study agent supplies prior to shipping to sites. However, for NRG-GY018, a matching placebo for pembrolizumab (MK-3475) is not available from the manufacturer. The blinding is integral to the conduct of the study and CTEP considers maintenance of the blind a significant contribution to the conduct of the study. Therefore, it is important to know who the responsible parties are for maintaining the blind and training appropriate staff at the site level. These individuals should not have direct contact with study subjects. Documentation of these significant contributors is through registration in the NCI's Registration and Credential Repository (RCR) and identification on the Delegation of tasks Log (DTL). NOTE: Registration in RCR may require the following documents, FDA 1572, NCI Biosketch, Financial Disclosure Form and documentation of Good Clinical Practice training.

Every site participating on NRG-GY018 must have at least two unblinded individuals available to manage study agent supplies. The unblinded personnel listed on the DTL must have an active CTEP-IAM user account and appropriate RCR person registration at the Investigator (IVR), Non-Physician Investigator (NPIVR) or Associate Plus (AP) level, be rostered at the site and be assigned the Unblinded Study Personnel task on the site DTL. At a minimum, this must include the site's Shipping Designee and at least one other site staff identified as responsible for overseeing the site agent management processes of; receiving blinded study agent from the NCI; managing the patient-specific DARF; preparing infusion solutions; and returning blinded study agent to the NCI. These individuals are responsible for training other Control and Satellite site dispensing area unblinded personnel if other staff involved in the process are not listed on the DTL. Study personnel assigned the tasks of "Unblinded Study Personnel" and "Investigational Product Accountability" on the DTL cannot be responsible for direct patient care or evaluation during the study in order to reduce the risk of unblinding treatment.

The external carton label of the pembrolizumab (MK-3475)/placebo package received from PMB is blinded, however, the **internal contents of each carton are not blinded**. It is the responsibility of the site staff to ensure the integrity of the blind at the site level. As a result, the number of staff members handling the study agent should be limited to the smallest number possible. A minimum of two individuals from the site (one of whom is the Shipping Designee) must be assigned the Unblinded Study Personnel task on the site DTL and sign the Pharmacy Agreement after reviewing the NRG-GY018 training materials. By signing the agreement, the signee is confirming to take actions appropriate to prevent unblinding patient and study personnel to a patient's treatment assignment. If all site personnel responsible for handling the study agent and maintaining the blind are not assigned on the DTL, a site level SOP must be in place documenting the steps and training to ensure the integrity of the blind at the site level. This documentation should include a list of trainees, dates of training and the signature of each trainee verifying training has been completed. The list (sample table provided by the Pharmaceutical Management Branch) must be available for review during an audit.

Each person to be designated on the DTL as Unblinded Study Personnel must read, understand and sign this Pharmacy Agreement. No study agent supplies will be shipped until at least two study personnel

from the site have signed Pharmacy Agreements and been assigned the Unblinded Study Personnel task on the DTL. Individuals assigned as Unblinded Study Personnel cannot hold any other tasks on the DTL except for Agent Accountability.

NRG-GY018 PHARMACY AGREEMENT **(21-MAY-2021) (09-MAR-2022) (30-SEP-2022) (24-FEB-2023)**

As of the unblinding of all patients on February 6, 2023, this Pharmacy Agreement no longer applies.

As a person holding the Unblinded Study Personnel task on the DTL, I agree to the following in the conduct of this clinical trial:

1. Participating study subjects, medical staff, ancillary medical staff, and data managers will remain blinded as to the study subject assignment of pembrolizumab (MK-3475) or Placebo until notified by NRG that assignments may be released.
2. Other site unblinded study personnel not identified on the DTL will be trained in the agent management processes for this study. As a DTL-designated Unblinded Study Personnel for my site I will oversee this training and document training of appropriate individuals (name and date of training) at the Control and any Satellite dispensing areas.
3. Only persons holding the Unblinded Study Personnel task on the DTL or persons trained by me and listed on my site training log will manage study agent supply (i.e., order, receive shipments, prepare infusions, maintain accountability logs, return or destroy unused supplies as directed by PMB).
4. Disposition of unused patient-specific Pembrolizumab (MK-3475) will be determined by the site's location:

    a. US Sites will return unused Pembrolizumab (MK-3475) or Saline Placebo to the NCI by the Unblinded Study Personnel or persons trained by me and listed on my site training log after the subject's protocol treatment is completed.

    b. Non-US (international) sites will request local destruction for any unused patient-specific Pembrolizumab (MK3475). One of the Unblinded Study Personnel or persons trained by me and listed on my site training log will submit the NCI Return Investigational Agent Form (available at https://ctep.cancer.gov/forms/) after the subject's protocol treatment is completed.

Name (print): _____

CTEP Person ID: _____

DTL Site Code (s): _____

DTL Institution Name(s):_____

Signature: _____ Date:_____

Complete the Pharmacy Agreement form and attach it as training documentation for the Unblinded Study Personnel task on the site DTL through the CTSU DTL module. Keep a copy for your records. Newly designated Unblinded Study Personnel must either complete and sign the Pharmacy Agreement and be added to the Delegation of Task Log or be trained by a site DTL-designated Unblinded Study Personnel and listed on the site training log as having received appropriate training on agent management processes for the study prior to handling the blinded study agents.

Sample Site Training Log

Trained Staff		**Unblinded Study Personnel***		
Printed Name	**Signature**	**Printed Name**	**Signature**	**Date of training**

* Must hold the Unblinded Study Personnel task designated on the site DTL

APPENDIX X - BIOSPECIMEN BANK-COLUMBUS FFPE MATERIALS VERIFICATION FORM

This form should be completed by the person in the pathology department who provides the FFPE materials to the requestor. ***Please return this form, along with the FFPE materials, to the requestor.*** *The requestor must include this completed form with the shipment of FFPE materials.*

REQUIRED FFPE MATERIALS

- **One** of the following archival tumor types must be submitted (listed in order or preference):
  - **persistent primary (FPP01)** or **persistent metastatic (FPM01)** tumor – i.e., collected prior to study treatment; lesion must not have been previously irradiated; or
  - **recurrent primary (FRP01)** or **recurrent metastatic (FRM01)** tumor – i.e., collected prior to study treatment; lesion must not have been previously irradiated; or
  - **primary (FP01)** or **metastatic (FM01)** tumor – i.e., collected prior to any treatment; lesion must not have been previously irradiated; or
  - **primary neoadjuvant (FPT01)** or **metastatic neoadjuvant (FMT01)** tumor – i.e., collected prior to any treatment; lesion must not have been previously irradiated. Only submit if tumor collected prior to any treatment is not available.
- Every attempt should be made to provide an FFPE block; however, if a block cannot be provided on a permanent basis, then 10 unstained slides (charged, 5µm) must be submitted.
- All tissue sections must be cut sequentially from **one** block.

PATIENT INFORMATION (to be completed by person requesting FFPE materials)

Patient ID: _____ **Bank ID:** _____

FFPE MATERIALS (to be completed by person preparing FFPE materials)

Surgical Pathology #: _____ **Block #:** _____ **Date Collected:** __ __ / __ __ / __ __ __ __

Tissue Type:
□ Persistent Primary (FPP01) □ Persistent Metastatic (FPM01)
□ Recurrent Primary (FRP01) □ Recurrent Metastatic (FRM01)
□ Primary (FP01) □ Metastatic (FM01)
□ Primary Neoadjuvant (FPT01) □ Metastatic Neoadjuvant (FMT01)

Site: □ Corpus Uteri □ Other, specify _____

Materials Prepared	**Number Provided**	**Thickness (µm)**
Block		**Not Applicable**
Charged slides		

_____
Name of person preparing materials Date

APPENDIX XI – PPD LABORATORY MANUAL (07/03/2019) (09/24/2019) (09-MAR-2022) (19-MAY-2022)

1. ORDERING PPD Supplies

PPD supplies will be ordered electronically. See Section 8.3.2. Please allow at least 7-10 business days for order requests to process. An additional 3-5 business days should be considered for delivery transit times. **Thus, please order PPD supplies at least 14 business days before they are needed.**

2. SUPPLIES PROVIDED

PPD will provide supplies required to collect, prepare, and ship the FFPE tissue slides required for the integral (MMR IHC) and exploratory PD-L1 IHC biomarker testing.

PPD Supplies contain:

- Package of slides
- Courier information and pre-printed airbills
- Shipping boxes and materials/gel packs
- The initial package is enough for 6 subjects

3. SHIPPING SAMPLES TO NEOGENOMICS

PPD supplies will include additional information regarding site shipment to NeoGenomics, Inc., including courier information and pre-printed airbills.

APPENDIX XII - MEDIDATA PATIENT CLOUD EPRO OPERATIONAL PROCEDURES (07/03/2019) (08-DEC-2020)

In this document *ePRO application* refers to the application accessed by the site via iMedidata and Rave, and *ePRO mobile app* refers to the app accessed by the patient on a mobile device.

1. Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata's ePRO application is preferred but not mandatory. Patients who will be submitting PRO data via the ePRO mobile app must be registered to the ePRO application by an authorized site staff after the patient has been registered to the study. Patients may use their own mobile device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to the ePRO mobile app with their passwords or their PIN codes on the same device.

2. ePRO Mobile Application Download

Note that there are multiple versions of the ePRO mobile app. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error upon logging into the ePRO mobile app if the wrong version is downloaded. The version being used on this trial is:

Patient Cloud

3. CRA Site Users

Site staff require access to the ePRO application. This access is granted through iMedidata, and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the ePRO application which they must accept in order to begin registering patients. Staff that have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. iMedidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU website under Data Management > Rave Home>Learn More About Rave > Medidata Account Activation and Study Invitation Acceptance. Site staff will not be able to access the study in the ePRO application until all required Rave and study specific trainings (eLearnings assigned in iMedidata) are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Data Management tab and further under the Rave subtab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4. CRA Instructions for Setting the Patient Cloud Mobile App to Multi-User Mode

Sites conducting studies entirely on-premises, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to the ePRO mobile app with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the ePRO mobile app to the device and set the ePRO mobile app to multi-user mode if applicable. **Verify the correct ePRO mobile app (Patient Cloud OR Patient Cloud ePRO) is downloaded per the protocol requirements. Note only 1 version of the app is active per protocol. On this protocol the app is named Patient Cloud and its icon is:

Patient Cloud

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

5. Patient Users

To use the ePRO mobile app, patients will need to use their own device (Apple iPhone or iPad, or Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to set up the tablet for multiple users. Multi-user mode lets multiple study participants log into the ePRO mobile app with their passwords or their PIN codes on the same device. **Refer to Section 4 above on Setting the Patient Cloud App to Multi-User Mode.**

6. Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO Mobile App

If you are using your personal device, and you do not have the ePRO mobile app with the icon shown below, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the ePRO mobile app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the ePRO mobile app available. Ensure that the correct version of the ePRO mobile

app is downloaded. For this study the app is named Patient Cloud and its icon looks like this:

Patient Cloud

You will need an email address that you agree to use for this purpose. The email address is needed to identify you on the ePRO Application, and to reset your password if needed. Your email address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an email address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS (when using an Apple device):

1. An Apple ID is required for downloading the ePROmobile app.
2. Tap the *App Store* icon on your device.
3. Search for the appropriate ePRO mobile app ("Patient Cloud," see the icon above) and follow the installation instructions.

For Android:

1. A Google account is required for downloading the ePRO mobile app.
2. Tap the *Play Store* icon.
3. Search for the appropriate ePRO mobile app ("Patient Cloud," see the icon above) and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the ePRO mobile app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the ePRO mobile app.

1. If registering from the ePRO mobile app, open the Patient Cloud app, tap **Register** on the bottom of the log in page. If registering on the web, open the URL https://shield.imedidata.com/ on a web browser.
2. Enter your activation code and tap **Activate**.
3. On the next page, read the instructions and tap **Next**.

4. Read the privacy notice and tap **I agree**. Then tap **OK** to confirm.
5. Enter and confirm your email address. Tap **Next**.
6. Enter and confirm your password. Tap **Next**.
7. **Choose a security question** by scrolling through the dropdown menu to display the question of your choice.
8. **Enter your response** to the security question.
9. Tap **Create my account** to complete your registration.

If you registered on the ePRO mobile app, it automatically logs you out. If you registered on the web, you are presented with the option to download the ePRO mobile app (Patient Cloud). You can then proceed to log in with the credentials you created.

Logging in to the ePRO mobile App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap **Log in**.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the ePRO mobile app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the ePRO mobile app (Patient Cloud). Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap **Yes** when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top right of most pages and selecting **Set PIN**.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu (3 vertical dots) on the top right of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top right of most pages.

1. Tap the options menu icon (3 vertical dots).
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged into the ePRO mobile app, forms related to your study are displayed on the Tasks

List page. Select a form, and complete and submit the form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

  To complete and submit form(s):

  1. Select the appropriate form.
  2. Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.
  3. If given the opportunity to review and update, review your responses by scrolling down the list; if you need to change an answer, tap the question to go back and change the answer.
  4. When you are ready to submit, tap **Submit Your Data**.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

7. Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

8. Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out, and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks “Submit,” the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC, and the patient accounts are hidden in iMedidata from sites and LPOs.

The ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

9. Site checklist for activities prior to consenting a patient

- ☐ Accept study invitation at iMedidata.com
  - Site staff must be rostered in RSS and have received an invitation to the ePRO application
- ☐ Site staff must have already completed required eLearning assigned in iMedidata for the ePRO application before gaining access to the study in Rave. Contact the LPO to request appropriate Rave access to register patients in the ePRO application.
- ☐ Verify the IOS or Android operating system is using the most current version
- ☐ Verify that the correct ePRO mobile app is being used. Note only 1 version of the ePRO mobile app is active per protocol.
- ☐ If using institutional shared devices, for the first patient only: Verify the ePRO mobile app is in Multi-User mode
- ☐ See the following webpage for more information about Patient Cloud iOS and Android ePRO apps. The landing page contains general information as well as links to additional resources on the left side of the screen https://learn.mdsol.com/patient-cloud/ecoa/en/get-started-with-patient-cloud-ios-and-android-apps-125282823.html

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to ePRO and also copy the correct image and name of the ePRO mobile app version with it to help remind staff and patients of the correct version being used in the protocol. The correct version for this protocol is named “Patient Cloud” and has an icon with a cloud and a sun.

☐

APPENDIX XIII – TREATMENT CONSIDERATIONS IN THE CONTEXT OF THE COVID-19 PANDEMIC AND PLACEBO DESIGN (14-OCT-2020)

The novel coronavirus has persisted in the United States. The virus is named "SARS-CoV-2" and the disease it causes has been named COVID-19. This outbreak has impacted health care delivery, with specific considerations in patients receiving anti-cancer directed therapy.

Given the potential impact of COVID-19 on the conduct of clinical trials, it has emerged as a priority to provide guidance to institutions in an effort to ensure patient safety, and appropriate clinical care. In 2020, the FDA issued a document on the conduct of clinical trials during the COVID-19 pandemic outlining important considerations. Importantly, the impact of COVID-19 on the conduct of clinical trials is anticipated to vary depending on several factors, including the nature of disease under study, the trial design, and in what region(s) the study is being conducted. Therefore, it is anticipated that institutions will develop different management strategies, based on clinical needs and available resources. Ultimately, the priority remains the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity.

NRG GY018 was designed as a placebo-controlled trial in order to preserve the integrity of the trial endpoint, while simultaneously examining a novel immunotherapy combination in patients with recurrent endometrial cancer and limited treatment options. The study team recognizes that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol. However, it is also clear that during some periods of time, in some geographic regions, administration of a placebo maintenance may not be feasible or deemed safe at an institution. Certainly, in regions where COVID-19 remains active, the risk/benefit balance may shift during the maintenance phase, supporting request for subject unblinding. Furthermore, institutional demands may necessitate temporary interruptions to subject accrual on trial, and it is anticipated that treatment sites will evaluate and mitigate on an individual level.

As such, the study protocol was amended to clarify that unblinding can be requested by the patient and/or the patient's treating physician because of safety concerns related to the COVID-19 pandemic as detailed in protocol section 5.2. The patient or treating physician can determine that safety of the patient is potentially compromised by COVID-19 in the patient's local/home area, areas of travel, or the office/treatment center. The patient can request unblinding after discussion with the treating physician. The treating physician must then request unblinding and notify the study PI. The patient should be encouraged to continue pembrolizumab maintenance if so assigned; patients may also elect to withdraw consent for treatment, but in that case, they are strongly encouraged to remain on study follow up (including maintenance of Radiologic Tumor Measurement schedule and Patient Reported Outcomes schedule per Tables 4.2 and 4.3). It is anticipated that all patients will continue in-person assessment and imaging reassessments on, or as close as possible to protocol directed intervals. The patient's request is to be respected whether or not the treating physician or study PI agree. The priority will be to assure the safety of trial participants while minimizing risk to trial integrity.

The study protocol was also revised to allow for Q6 week administration of pembrolizumab (MK-3475) or placebo in the maintenance phase. This was done with an intent to reduce the number of visits to the infusion center during the COVID-19 pandemic. We encourage investigators to make every effort to try and coordinate office, imaging and infusion visits as permitted based on the protocol specified timelines, in order to reduce the burden on participating patients, and possible COVID-19 exposures.

APPENDIX XIV: COUNTRY-SPECIFIC APPENDIX – JAPAN (09-MAR-2022) (19-MAY-2022) (24-FEB-2023)

Eligibility

Section 3.2.1: If standard of practice in Japan is to not do local/institutional IHC testing for MMR, then centralized testing results will be used, and the pathology report does not have to include results of institutional MMR IHC testing.

Assessments

Section 4.1: institutional mismatch repair protein IHC results are not required for patients enrolled in Japan.

Section 4.2: Chemistries: Bicarbonate is not required for patients enrolled in Japan

Centralized MMR IHC Testing/Return of Results/Step 2 Randomization

Sections 5.7, 8.3.3, 10.2.1, 10.2.4

Sites in Japan with institutional MMR IHC results may use those results for Step 2 Randomization, after submission of additional slides to Neogenomics for centralized MMR IHC testing.

Sites in Japan with MMR IHC results previously reported from Neogenomics can use those results to fulfill both local and centralized MMR IHC testing requirements for NRG-GY018.

When NRG-GY018 centralized MMR IHC testing results through Neogenomics are the only MMR IHC results available, sites must wait until the patient's centralized results are returned to proceed to Step 2 randomization.

Please note:

- Testing turnaround time is 7 business days from the day the sample is received by NeoGenomics. Please plan accordingly.
- Do not contact Neogenomics for MMR IHC result status before 7 business days have elapsed since receipt of samples.

  NeoGenomics Laboratories, Inc.
  Attn: Pharma Services Dept.
  31 Columbia
  Aliso Viejo, CA 92656
  Email: pharma_project_support_team@neogenomics.com
  Phone: 949-445-7300, x7103

- MMR IHC results will be reported to the NRG SDMC and can be found in the Pre-Entry folder in Rave.
- Please see the "Confirmation to Proceed to Step 2" form in the Pre-Entry folder in Rave. This is the notification that you can proceed after the MMR IHC result is reported.

Investigational Drug Supply/Placebo

- Pembrolizumab placebo infusions will be prepared without the addition of saline from vials provided by PMB.
- A shipment containing an empty carton will be sent for initial orders. A memo instructing sites how to prepare pembrolizumab placebo infusions will be placed in an empty carton. The carton will be sealed, and the two-part, patient-specific label attached to the outside. The small, patient ID label will be affixed to the memo, prior to its insertion into the empty carton.
- PMB will continue to provide placebo shipments (preparation memo inside an empty carton) while patients randomized to the placebo arm are receiving treatment.
- Unblinded study personnel at the site are responsible for submitting an order, timing its submission so the shipment is received not more than 4 weeks prior to next scheduled dose.

Effective February 06, 2023, all patients were unblinded. Patients randomized to placebo (Arm 1) will not receive additional placebo infusions. All other study related treatments and evaluations will proceed per protocol.