Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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Study Enrollment Criteria: Eligible Patients

1. Patients must have had 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.

All patients were required to have histologic confirmation of the original primary tumor (submission of pathology report(s) is required). Patients with the following histologic types were eligible: endometrioid adenocarcinoma, serous adenocarcinoma, dedifferentiated/undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.).

Submission of tumor specimens for centralized MMR IHC testing was required after Step 1 and before Step 2 registration.

2. In patients with measurable disease, lesions were defined and monitored by RECIST v1.1. Measurable disease was defined as at least one lesion that could be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion was required to be ≥10 mm when measured by CT or MRI. Lymph nodes were required to be ≥15 mm in short axis when measured by CT or MRI.

3. Prior Therapy:
• Patients were permitted to have received:
    a. No prior chemotherapy for treatment of endometrial cancer OR
    b. 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 have been 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 have been 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, was NOT permitted.

4. Age ≥18 years

5. Performance status of 0, 1 or 2

6. Adequate hematologic function defined as follows:
    a. Platelets ≥100,000/mcl

b. Absolute neutrophil count (ANC) ≥1,500/mcl

7. Adequate renal function defined as follows: creatinine ≤1.5x institutional/laboratory upper limit of normal (ULN)

8. Adequate hepatic function defined as follows: total serum bilirubin level ≤1.5x ULN (patients with known Gilbert's disease who have bilirubin level ≤3x ULN may be enrolled)

a. AST and ALT ≤3x ULN

9. TSH within normal limits. If TSH was not within normal range despite no symptoms of thyroid dysfunction, normal Free T4 level was required.

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

11. For patients of childbearing potential: negative urine or serum pregnancy test. If the urine test was positive or could not be confirmed as negative, a serum pregnancy test was required.

12. Patients with a prior or concurrent malignancy whose natural history or treatment did not have the potential to interfere with the safety or efficacy assessment of the investigational regimen were eligible for this trial.

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

Study Enrollment Criteria: Ineligible Patients

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

2. Patients with 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.

3. Patients who were currently participating and receiving cancer-directed study therapy or who participated in a study of an investigational agent and received cancer-directed study therapy within 4 weeks prior to Step 2 registration.

4. Patients with a diagnosis of immunodeficiency or who received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to Step 2 registration.
• Patients who received steroids as CT scan contrast premedication were permitted to be enrolled.
• The use of inhaled or topical corticosteroids was allowed.
• The use of mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency was allowed.
• The use of physiologic doses of corticosteroids may have been approved after consultation with the study chair.

5. Patients with treated brain metastases were eligible if follow-up brain imaging after CNS-directed therapy showed no evidence of progression, and they were off steroids for at least 4 weeks prior to Step 2 registration and remained clinically stable.

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 included, but was 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 were 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 required evaluation for the presence of target organ involvement and potential need for systemic treatment but would otherwise be eligible.

7. Patients with a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

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.

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 have been 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 were currently on treatment, they were eligible if they had an undetectable HCV viral load.

10. Pregnant or lactating patients.

International Federation of Gynecology and Obstetrics (FIGO) Stage Grouping for Primary Endometrial Cancer (2009)[1]

In this protocol, patients were required to have measurable stage III, measurable stage IVA, stage IVB (with or without measurable disease), or recurrent (with or without measurable disease) endometrial cancer.

Stage IA: Tumor confined to the uterus, <50% myometrial invasion

Stage IB: Tumor confined to the uterus, <50% myometrial invasion

Stage II: Cervical stromal invasion

Stage IIIA: Tumor invasion into the serosa or adnexa

Stage IIIB: Tumor involving the vagina or parametria

Stage IIIC1: Pelvic lymph node involvement

Stage IIIC2: Paraaortic lymph node involvement

Stage IVA: Tumor invasion into the bladder or bowel mucosa

Stage IVB: Distant metastases (including abdominal metastases) or inguinal lymph node involvement

Eastern Cooperative Oncology Group (ECOG) Performance Status[2]

0 – Fully active, able to carry on all pre-disease performance without restriction.

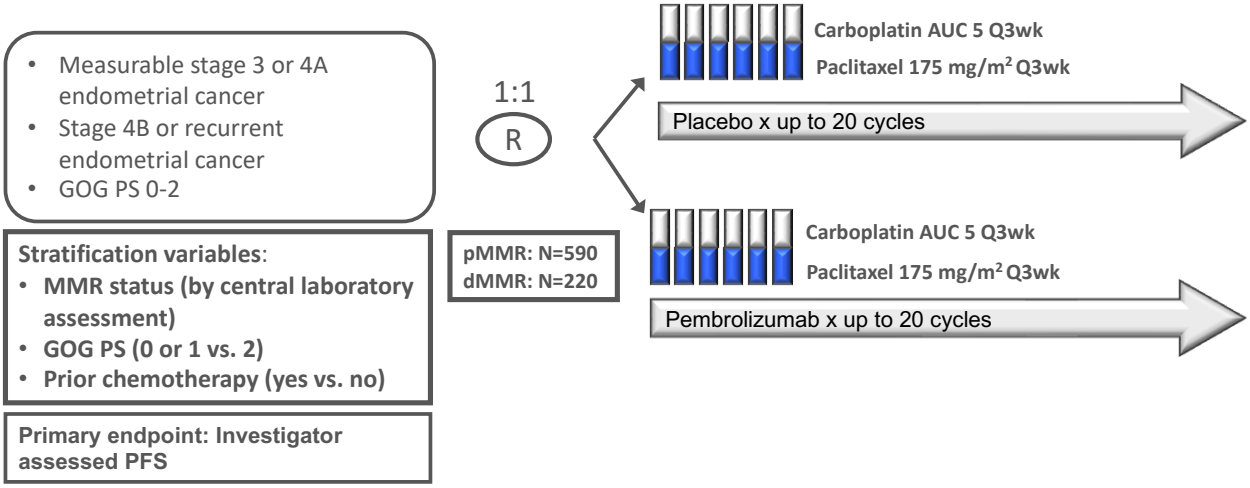
1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.

2 – Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 – Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.

4 – Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair.

Protocol Schema



Assessment of Disease Response: RECIST v1.1

Antitumor Effect – Solid Tumors

Response and progression were evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).[3] 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.

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.

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 did not allow PET-CT use for RECIST v1.1 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.

Response Criteria

Determination of response should take into consideration all target and non-target lesions

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.

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).

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

Adverse Event Reporting on Trial

This study utilized 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 were advised to have access to a copy of the CTCAE version 5.0.

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.

Comprehensive Adverse Events and Potential Risks (CAEPR) for MK 3475 (pembrolizumab, NSC 776864) (27-FEB-2020)

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 MK-3475 (pembrolizumab).

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.

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (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]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	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]		
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]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK 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)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	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]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		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		
	Pleuritic pain[2]		
	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 MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

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

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) 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 - 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; 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; 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: MK-3475 (pembrolizumab) 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.

Adverse Events for Commercial Study Agents

Sites and treating investigators were referred to the package insert for detailed pharmacologic and safety information.

Regulatory Approval Timeline and Conduct of NRG GY018

January 2017 – August 2017:	Trial design and approval by the Uterine Corpus Committee (NRG Oncology), Protocol Development Committee (NRG), Uterine Task Force (NCI), Gynecologic Cancer Steering Committee (NCI)
July 16, 2019	Trial activated
April 2020 – Nov 2020	Trial accrual paused due to COVID-19 pandemic and public health crisis to permit implementation of strategies to mitigate patient risk given the placebo-controlled nature of the trial
August 2022	Mismatch repair-deficient (dMMR) cohort target accrual reached (N = 225)
December 2022	Mismatch repair-proficient (pMMR) cohort target accrual reached (N=591)
December 2, 2022	Analysis dataset closure occurred for the pMMR endometrial cancer cohort (futility)
December 6, 2022	Analysis dataset closure occurred for the pMMR endometrial cancer cohort (efficacy endpoint)
December 16, 2022	Analysis dataset closure occurred for the dMMR endometrial cancer cohort (futility and efficacy endpoint)
January 26, 2023	Release of data by NCI DSMB and NRG Oncology concerning the superiority of the pembrolizumab containing regimens

NRG GY018 Press Release, February 2, 2023

NRG Oncology NRG-GY018 Study Demonstrates Significantly Improved Progression Free Survival Outcomes for Women with Advanced or Recurrent Endometrial Cancer with the Addition of Pembrolizumab to Chemotherapy

February 03 2023

NRG Oncology Phase III clinical trial, NRG-GY018, evaluating pembrolizumab in combination with standard of care chemotherapy (carboplatin and paclitaxel) met its primary endpoint of progression free survival (PFS) for the treatment of patients with stage III-IV or recurrent endometrial carcinoma, regardless of mismatch repair status. A pre-specified interim analysis, conducted by an independent Data Monitoring Committee, demonstrates that pembrolizumab in combination with chemotherapy has a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy alone in both study cohorts, mismatch repair deficient (dMMR) and mismatch repair proficient (pMMR). The full results of this trial will be presented at an upcoming scientific conference.

NRG-GY018, a randomized, blinded, placebo-controlled study, accrued 819 women with stage III-IV or recurrent endometrial cancer. Two independent cohorts were evaluated, patients with endometrial cancers that are dMMR and patients with endometrial cancers that are pMMR. Patients were randomly assigned to receive pembrolizumab combined with carboplatin and paclitaxel (for a planned six, 3-week cycles), followed by pembrolizumab maintenance (for up to fourteen, 6 week cycles) or placebo combined with carboplatin and paclitaxel, followed by placebo maintenance.

“Patients with advanced stage or recurrent endometrial cancer, the most common type of gynecologic cancer in the U.S., face a poor prognosis with limited treatment options. This is particularly notable in patients who progress after prior platinum-based adjuvant therapy with disease not amenable to curative surgery or radiation,” stated Ramez Eskander, MD, of the University of California San Diego Moores Cancer Center and the Principal Investigator of the NRG-GY018 trial. “In this study, pembrolizumab in combination with carboplatin and paclitaxel resulted in a statistically significant and clinically meaningful improvement in PFS in both the dMMR and pMMR study populations.We look forward to presenting these exciting findings at an upcoming scientific congress.”

This project was supported by the NRG Oncology Operations grant U10CA180868 and the NRG Oncology SDMC grant U10CA180822 from the National Cancer Institute (NCI), part of the National Institutes of Health and conducted by the NCI National Clinical Trials Network. Funding and support were also received from Merck & Co., Inc. through a Cooperative Research and Developmental Agreement with NCI.NRG-GY018 was conducted with funding supplemental to the CRADA from Merck in an Agreement between Merck and The GOG Foundation d/b/a NRG Oncology Philadelphia East.

About NRG Oncology

NRG Oncology conducts practice-changing, multi-institutional clinical and translational research to improve the lives of patients with cancer. Founded in 2012, NRG Oncology is a

Pennsylvania-based nonprofit corporation that integrates the research of the legacy National Surgical Adjuvant Breast and Bowel Project (NSABP), Radiation Therapy Oncology Group (RTOG), and Gynecologic Oncology Group (GOG) programs. The research network seeks to carry out clinical trials with emphases on gender-specific malignancies, including gynecologic, breast, and prostate cancers, and on localized or locally advanced cancers of all types. NRG Oncology's extensive research organization comprises multidisciplinary investigators, including medical oncologists, radiation oncologists, surgeons, physicists, pathologists, and statisticians, and encompasses more than 1,300 research sites located world-wide with predominance in the United States and Canada. NRG Oncology is supported primarily through grants from the National Cancer Institute (NCI), part of the National Institutes of Health, and is one of five research groups in the NCI's National Clinical Trials Network.

NRG Oncology Dear Investigator Letter

February 3, 2023

Dear Investigator:

You are receiving this letter because you have participated in and are currently treating a patient on **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.**"

The purpose of this letter is to inform you that a protocol pre-specified interim analysis, conducted by the independent Data Monitoring Committee (DMC), demonstrated that pembrolizumab in combination with chemotherapy has a statistically significant and clinically meaningful improvement in progression free survival (PFS) compared with chemotherapy alone in both study cohorts, mismatch repair deficient (dMMR) and mismatch repair proficient (pMMR).

Due to the availability of these results, the treatment assignment for all study participants will be unblinded. Treating investigators will inform patients of their treatment assignment. Unblinded patients on the placebo arm in the combination phase of the trial should continue to receive carboplatin and paclitaxel as directed by the study and discontinue placebo infusions. If patients are in the maintenance phase, they will discontinue placebo infusions, and continue required study assessments.

Study participants receiving pembrolizumab will complete study directed treatment with pembrolizumab.

All participants will remain on study, and follow the required study assessments (see sections 4.2 and 4.3).

As of February 3, 2023, the unblinded treatment information can be found in the patient's chart in Medidata Rave in the Enrollment Forms folder on the Treatment Assignment Form. Details on reporting discontinuation of placebo will be shared in a later communication.

On behalf of NRG Oncology, the three Group Chairs, and the National Cancer Institute, we want to thank you and your patient for participating in this important clinical trial.

Sincerely,

Robert S. Mannel, MD NRG Oncology
Group Chair

Robert S. Mannel, MD

NRG Oncology Dear Patient Letter

Dear Patient:

You are receiving this letter because you have participated in and are currently receiving treatment on 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."**

The purpose of this letter is to inform you that a pre-planned interim analysis has just been completed. It reveals that the addition of pembrolizumab to chemotherapy (carboplatin and paclitaxel) slows the time to cancer progression. Now that these results are available, the use of the placebo infusions is no longer necessary.

Your doctor will inform you of your blinded treatment assignment and discuss with you the management of your future care. If you are receiving placebo infusions, you will no longer need to receive these. If you are receiving pembrolizumab infusions, you should continue treatment per the study. We ask all patients to continue to have follow up visits to evaluate the safety of treatment and to continue scans to monitor the effect of treatment on your disease according to the study plan. We ask you to continue to complete your patient reported outcome and Quality of Life questionnaires.

On behalf of NRG Oncology, the three Group Chairs, and the National Cancer Institute, I want to thank you sincerely for your participation in this important clinical trial and your commitment to discovering better treatments for endometrial cancer and to wish you improved health.

Gratefully,

Robert S. Mannel, MD NRG Oncology
Group Chair

Supplementary Figures

Figure S1A: Shown here are Kaplan-Meier interim overall survival futility estimates in the population of patients with advanced-stage or recurrent endometrial cancer with mismatch repair-deficient (dMMR) disease, inclusive of curve with 95% pointwise confidence intervals.

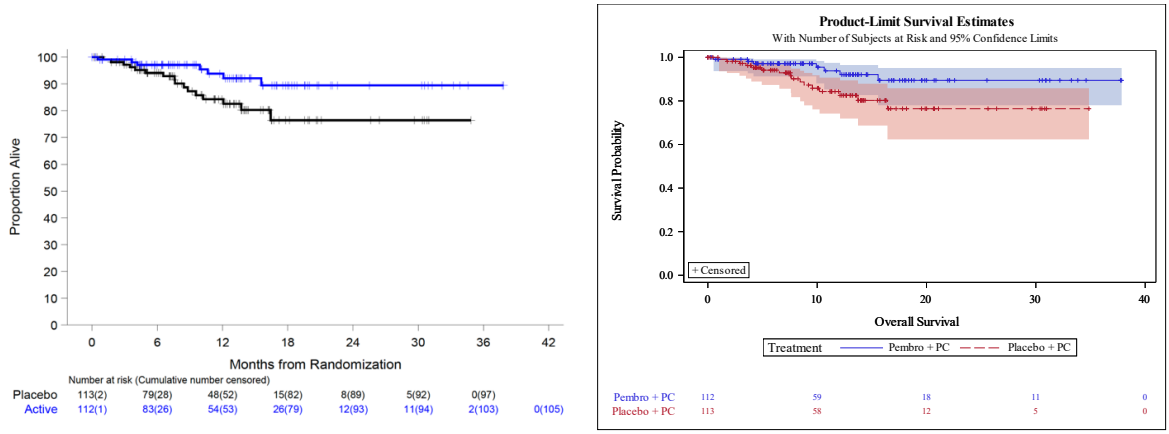


Figure S1B: Shown here are Kaplan-Meier interim overall survival futility estimates in the population of patients with advanced-stage or recurrent endometrial cancer with mismatch repair-proficient (pMMR) disease, inclusive of curve with 95% pointwise confidence intervals.

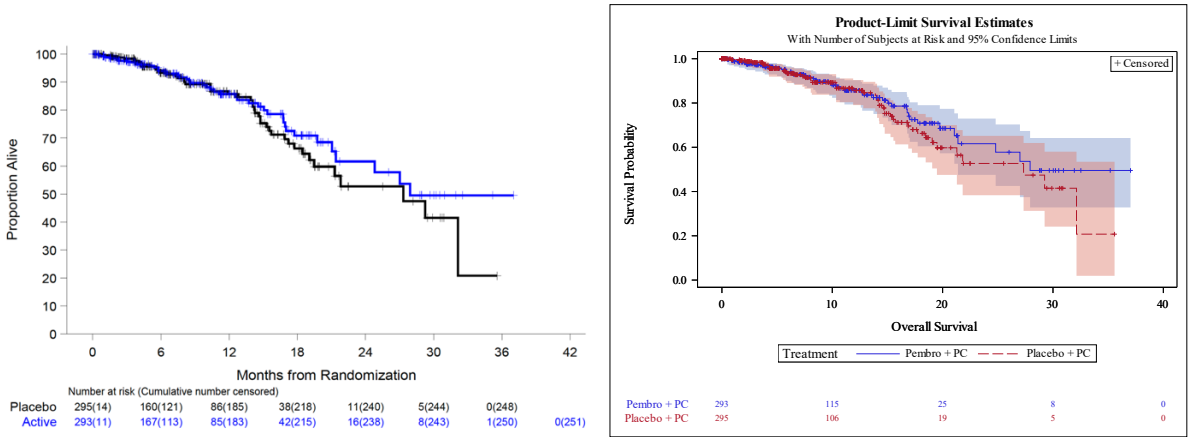
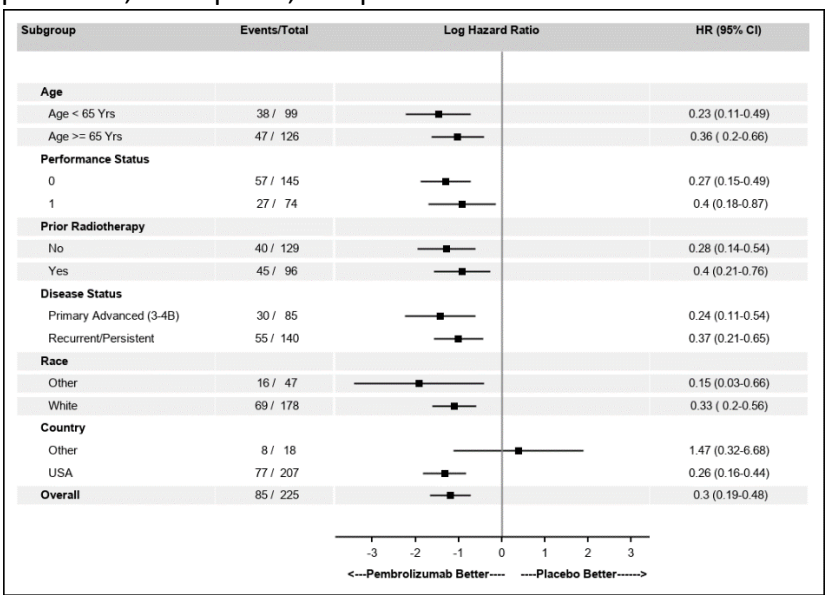
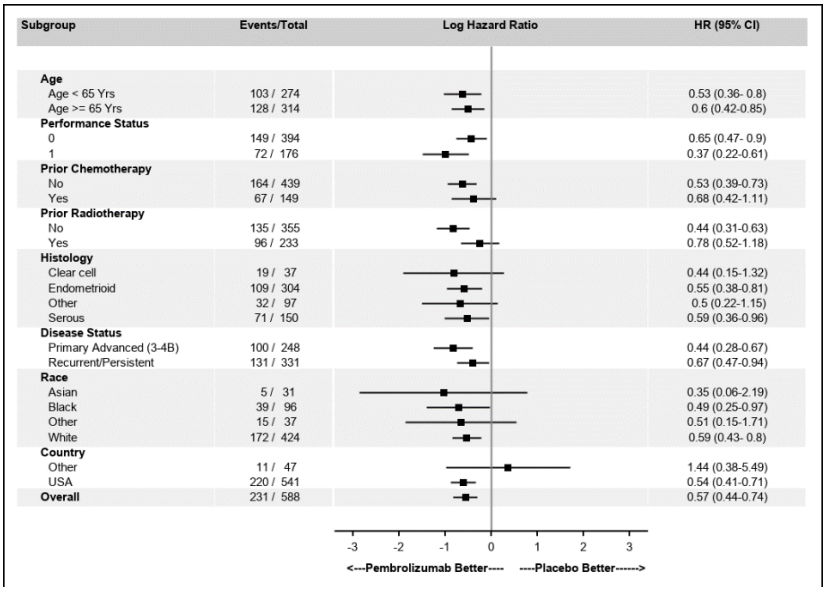


Figure S2A: Shown here is an analysis of progression-free survival in key dMMR endometrial cancer patient subgroups. Patients in the pembrolizumab-combination group received paclitaxel, carboplatin, and pembrolizumab; those in the placebo-combination group received paclitaxel, carboplatin, and placebo.*



*Confidence intervals should not be used to reject or not reject the null hypothesis of a treatment effect. Reported confidence interval for "other countries" is not accurate due to small number of patients.

Figure S2B: Shown here is an analysis of progression-free survival in key pMMR endometrial cancer patient subgroups. Patients in the pembrolizumab-combination group received paclitaxel, carboplatin, and pembrolizumab; those in the placebo-combination group received paclitaxel, carboplatin, and placebo.*



*Confidence intervals should not be used to reject or not reject the null hypothesis of a treatment effect. Given only 18 patients had ECOG performance status of 2, these were excluded from the above analysis. Nine patients without known disease status were also excluded.

Figure S3: Shown here are Kaplan-Meier progression-free survival estimates in the entire study population of patients with advanced-stage or recurrent endometrial cancer (both mismatch repair-proficient [pMMR] and mismatch repair deficient [dMMR] disease).

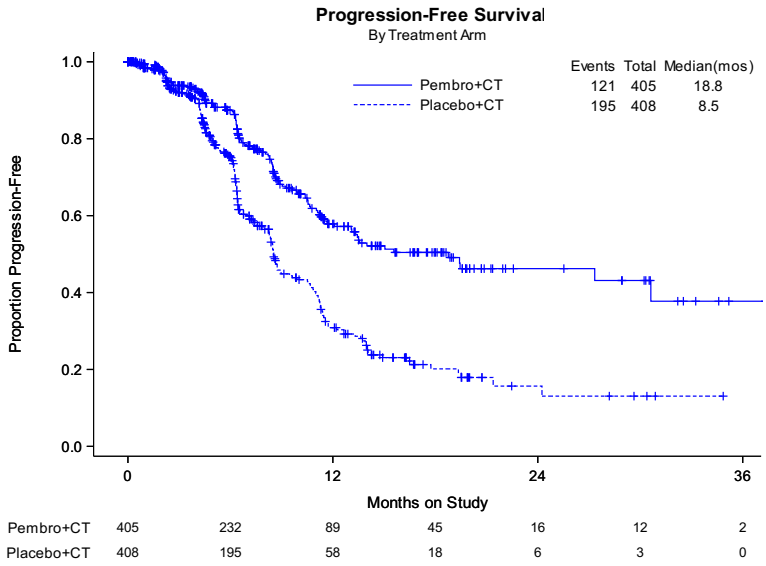
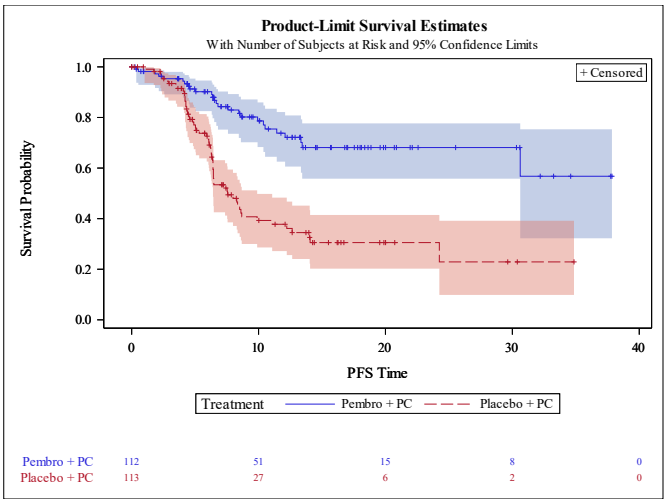


Figure S4A: Shown here is the Kaplan-Meier estimate of progression-free survival in the population of patients with advanced-stage or recurrent endometrial cancer with mismatch repair-deficient (dMMR) disease. Tick marks in Panel A indicate censoring of data. Included are 95% pointwise confidence intervals.



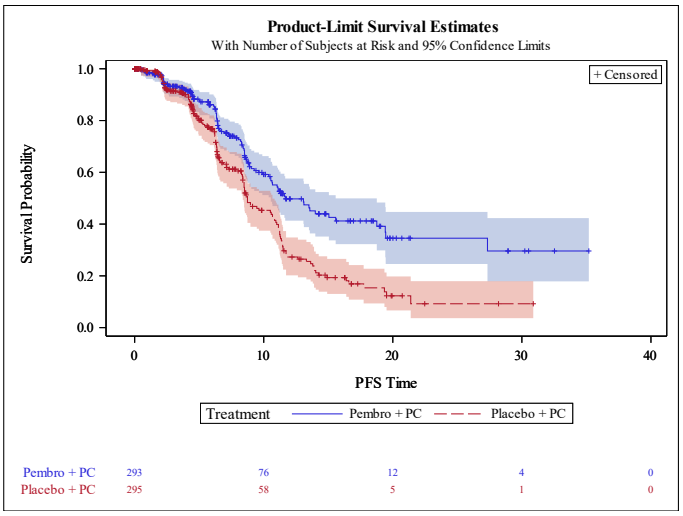
dMMR

PFS

Pembro
10%ile (95%)
6.31 2.56 – 7.59

Placebo
10%ile (95%)
4.14 2.40 – 4.30

Figure S4B: Shown here is the Kaplan-Meier estimate of progression-free survival in the population of patients with advanced-stage or recurrent endometrial cancer with mismatch repair-proficient (pMMR) disease. Tick marks in Panel A indicate censoring of data. Included are 95% pointwise confidence intervals.



pMMR

PFS

Pembro
10%ile (95%)
4.44 2.63 - 6.11

Placebo
10%ile (95%)
4.17 2.30 – 4.40

Supplementary Table

Table S1: Disease assessment methods and schedule.

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

[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 were obtained until disease progression was confirmed; at the investigator's discretion, imaging could be repeated at any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. Physicians were instructed to utilize the **same** imaging modality of the abdomen, pelvis and chest as for pre-cycle 1 baseline assessment. **PET/CT was NOT to be used for any disease assessment or reassessment.** Images from radiographic studies was uploaded for independent radiologic review via TRIAD Digital Image Submission.

[4] PROs assessment intervals were to occur: Week 0, Week 6, Week 18, Week 30, Week 54. PRO assessments were required, even after a patient was removed from treatment.

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

References

1. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009; 105(2):109.

2. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Author Contributions

The first draft of the manuscript was written by Ramez N. Eskander, and subsequently reviewed and edited by senior author, Dr. Carol Aghajanian, followed by all other co-authors. No writing assistance was received.