

A Phase 2 study of a Checkpoint Inhibitor in Men with Progressive Metastatic Castrate Resistant Prostate Cancer Characterized by a Mismatch Repair Deficiency or Biallelic CDK12 Inactivation

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Department of Veterans Affairs

RESEARCH CONSENT FORM

Version Date: September 18, 2019

Participant Name

Date: 3/10/20

Title of Study: A Single-arm, Open-label, Phase II Study of Checkpoint Inhibitors in Men with Progressive Metastatic Castrate Resistant Prostate Cancer Characterized by a Mismatch Repair Deficiency or Biallelic CDK12 Inactivation (CHOMP)

Principal Investigator: Matthew Rettig, MDVA Facility: VA GLAHS – West LAPrincipal Investigator for Multisite Study: Matthew Rettig, MD

MAIN INFORMED CONSENT SUMMARY

You are being invited to take part in a research study that is being funded by the Department of Veteran Affairs. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

Read the information below closely and discuss it with family and friends if you wish. Ask one of the study staff if there is anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you have received all the information below and were able to discuss any questions and concerns you had with a study team member.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

The purpose of this study is to determine the efficacy of an immune therapy known as pembrolizumab in patients with metastatic castration resistant prostate cancer (mCRPC) characterized by a specific genetic mutation (mismatch repair deficiency or inactivation of CDK12). Pembrolizumab is already FDA approved for patients who have metastatic malignancies with mismatch repair deficiency and have progressed on standard therapies, so the use of pembrolizumab for patients with mismatch repair deficiency is consistent with labeling indications and not investigational. Pembrolizumab has not been formally tested in patients with CDK12 inactivation.

Prior to starting treatment, you will undergo a genetic test to determine if you have a mutation in your tumor tissue that the study investigators believe will make your cancer responsive to pembrolizumab. Your tumor tissue and/or blood specimen will be tested for the presence of one of the following two tumor mutations by a commercial lab known: mismatch repair deficiency and CDK12 inactivation. If your test results indicate that your tumor has either a mismatch repair deficiency or inactivation of CDK12, you may be eligible to participate in the main study and receive the immunotherapy drug pembrolizumab.

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VA Facility: VA GLAHS – West LA

Principal Investigator for Multisite Study: Matthew Rettig, MD

Patients who meet the eligibility criteria will receive pembrolizumab intravenously every three weeks until the cancer gets worse (i.e. the cancer progresses) or unacceptable side effects. Patients will remain on therapy that suppresses the blood testosterone (male hormone) levels as would be done per routine care. Patients will undergo two biopsies of a metastasis: one prior to treatment and one at the time the cancer progresses to determine how the cancer may become resistant to the treatment.

We hope to discover how patients with mCRPC respond to immunotherapy, which has been widely successful for other cancers. This can lead to a novel therapy that is different from the current approaches to treating prostate cancer. Although the study drug, pembrolizumab has been approved for patients with mismatch repair deficiency, it has not been formally tested in patients with CDK12 inactivation. We are doing further testing in mismatch repair deficient patients to determine the efficacy in Veterans. By performing the biopsies before pembrolizumab and when you are taken off pembrolizumab, we plan to identify the underlying explanation for why some patients who have either mismatch repair deficiency or CDK12 inactivation do not respond in the first place or initially respond but then become resistant to pembrolizumab.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

There is no guarantee that you will directly or personally benefit from this study. Having your blood or tumor tissue specimens tested may help determine whether your tumor has the genetic mutations that predict sensitivity to pembrolizumab. It is also possible that taking pembrolizumab may delay cancer progression and extend your life. Moreover, the knowledge obtained from this study may help treat other patients with your condition in the future.

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WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

There is no guarantee that you will benefit from taking pembrolizumab. It is possible that the study drug and procedures may lead to adverse side-effects or may not prevent cancer growth. For a complete description of risks, refer to the Detailed Consent below.

This study is completely voluntary, and you do not have to take part in it. The study doctor will discuss alternative treatments for your prostate cancer and the risks and benefits of each option.

DO YOU HAVE TO TAKE PART IN THE STUDY?

You do not have to take part in this study. If you decide to take part in this study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Dr. Matthew Rettig, MD at the VA Greater Los Angeles Healthcare System. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, please contact Dr. Matthew Rettig, MD at 310-478-3711 ext. 44761 or the study coordinator, Sage Pitcher, at 310-478-3711 ext. 41156.

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MAIN INFORMED CONSENT

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to determine the efficacy of pembrolizumab in patients with metastatic castration resistant prostate cancer (mCRPC) characterized by a specific genetic mutation (mismatch repair deficiency or inactivation of CDK12). Additionally, these patients must have progressed on at least one of the new hormone therapies for advanced prostate cancer, such as abiraterone acetate (Zytiga), enzalutamide (Xtandi), or apalutamide (Erleada).

Pembrolizumab is a FDA approved checkpoint inhibitor (a form of immunotherapy) for the treatment of various cancers, such as melanoma and non-small cell lung cancer. It works by overcoming the ability of tumor cells to block the immune system from attacking the tumor. Based on previous studies, only about 10-15% of patients with mCRPC are responsive to checkpoint inhibitors. If a checkpoint inhibitor like pembrolizumab is used to treat *all* patients, most patients would not respond to the treatment and therefore would only be exposed to the side effects of the treatment without the tumor responding. Based on research that has already been done, it is believed that the response to pembrolizumab is higher in patients with either mismatch repair deficiency or inactivation of CDK12, one of which has been detected in your tumor.

Patients who meet the eligibility criteria will receive pembrolizumab intravenously every three weeks along with an ongoing therapy to suppress male hormone levels until the cancer progresses (i.e. gets worse) or unacceptable toxicity (i.e. unacceptable side effects). Pembrolizumab is FDA approved for patients who have metastatic malignancies with mismatch repair deficiency and have progressed on standard therapies. As a result, this study drug is consistent with labeling indications and not investigational.

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Patients will also undergo two biopsies and research blood draws. Prior to initiating treatment with pembrolizumab, patients will undergo a baseline biopsy of a metastatic lesion to detect genetic mutations if a specimen is not already available. Blood will also be collected to analyze circulating tumor DNA (ctDNA), which is the DNA that is shed into the bloodstream by your tumor. A second biopsy of a metastasis will be obtained at the time of cancer progression. By comparing these two biopsies, the investigators plan to identify the underlying molecular explanation as to why patients did not respond in the first place or responded and then became resistant to pembrolizumab. Blood will also be collected periodically throughout the treatment to identify other molecular correlates for research purposes.

By conducting this research project, we hope to learn the following:

- Effects of pembrolizumab on your prostate cancer.
- Molecular clues and patterns of resistance and sensitivity to pembrolizumab.
- Effects of specific genetic mutations on pembrolizumab activity.
- Response rate of pembrolizumab in Veterans with prostate cancer who have mismatch repair deficiency or CDK12 inactivation.
- How you feel when taking pembrolizumab.

We hope to discover how patients with mCRPC respond to immunotherapy. This study can lead to a novel therapy that is different from the current hormonal approach to treating prostate cancer.

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HOW LONG WILL I BE IN THE STUDY?

This research study is divided into three phases:

- Screening phase will determine if you are eligible for the study. If you qualify, you will begin treatment.
 - Genetic screening: This involves testing the genetic material from your tumor to determine if your tumor contains one of the genetic mutations that the research team thinks will make your tumor sensitive to the pembrolizumab. The tumor tissue can come from one of three sources:
 - Blood
 - Archived tissue (e.g. a prostate biopsy or prostate surgical specimen)
 - Fresh biopsy of a metastasis.
 - Other screening studies:
 - Blood tests, physical exam, history, vital signs must be completed within 28 days of starting the pembrolizumab.
 - Scans (e.g. CT scans and bone scans) must be completed within 60 days of starting pembrolizumab.
 - A baseline biopsy (prior to starting pembrolizumab) of a metastasis will be performed unless a metastatic biopsy was previously performed within 180 days of the first pembrolizumab dose.
- Treatment phase (continuous dosing of pembrolizumab)
 - You will continue taking pembrolizumab every three weeks until clinical progression or unacceptable toxicity.
- A second biopsy of a metastasis within 45 days of the last pembrolizumab dose.

This research study is expected to take approximately 4 years. Your individual participation in the project will take approximately 36 months.

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WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

Before you begin the study:

After you sign this consent form, you will undergo certain screening tests including blood work and scans to determine if you can be in the study. Your blood and tumor tissue specimens will be collected and sent to a commercial vendor for genetic screening if not already performed. If you already have a sample of the metastatic lesion from a previous biopsy, this sample may suffice for testing and you may not need to undergo another biopsy. Your specimens will be tested to determine if you have either a mismatch repair deficiency or inactivation of CDK12.

If you have not had genetic testing of your tumor tissue, then the baseline biopsy of a metastatic lesion is not purely research. In this situation, the collection and testing of one or two samples of tumor tissue is part of your regular medical care. However, we will collect and test additional samples obtained from the same procedure at the same location for research purposes. If you have a readily available metastatic specimen for testing that was performed within 180 days of your starting pembrolizumab, then you may not need to undergo the baseline biopsy; your study doctor will discuss with you further if the specimen will suffice for testing depending on its type, quality, and quantity.

Additionally, the other screening tests (e.g. blood tests and scans) that are required to determine your eligibility for the study may be done on one or more days, but they will all be completed prior to starting treatment with pembrolizumab: within 28 days for blood and within 60 days for scans. Some of these examinations or procedures may be part of your regular medical care. If you have completed some of the tests recently, then you do not need to repeat them. The study staff will let you know what tests need to be completed. It is possible that you may not be eligible for this study after taking these tests.

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The following table shows which screening procedures are standard of care (SOC) versus research.

Standard of Care	Research
Medical history review	Research blood
Physical exam	Biopsy of a metastatic lesion (pre- and post-treatment)
Vitals and ECOG	
Clinical laboratory panel (blood and PSA)	
Tumor assessment via CT/MRI/Bone scan	

The chart below shows the tests and procedures that will occur during the screening period.

VISIT	WHAT HAPPENS
Genetic Screening Phase (Any time prior to study enrollment)	• Read this informed consent form and ask any questions you may have. If you wish to participate in this research, sign this form. • Undergo the following specimen collection: ○ Blood, archived tissue, or metastatic biopsy specimen for genetic analysis to determine if you have the genetic mutations that will allow you to receive the pembrolizumab as a part of this study. The sources of tumor tissue for genetic analysis include: ▪ Up to approximately 2 tablespoons of blood. ▪ An archived specimen (e.g. prostate surgery specimen) can be used if available. ▪ Alternatively, a metastatic biopsy can be used for genetic analysis. This specimen can be archived or obtained for the purpose of this study. ○ Tumor tissue from a biopsy of a metastatic lesion. Your study doctor will explain to you the specific type of biopsy that would be performed based on the size and location of your tumor. Up to 8 samples will be collected. One or more

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samples obtained from this biopsy may be used for genetic sequencing as part of standard management (genetic sequencing is considered a standard of care procedure). The remaining samples will be used for more extensive research testing to learn more about your cancer that could inform the researchers about how to treat prostate cancer patients in the future. This biopsy procedure will be performed even if genetic analysis of your tumor was performed on another source of tumor tissue, **unless the source of tumor tissue was a biopsy performed within 180 days of your planned pembrolizumab start date.**

- If you already have a sample of metastatic lesion from a previous biopsy that is sufficient for testing and analysis, you will not need to undergo another biopsy.
- Confirm that your cancer has either a mismatch repair deficiency or a biallelic inactivation of CDK12 by submitting the above-mentioned specimens to a commercial vendor for genetic testing.
 - Genetic testing performed on one sample may give different results than one performed on another sample. For example, the tumor issue test may find certain mutations that are absent in the blood test. These differences will be discussed with you by your study doctor and staff.

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Screening Phase

(28 days prior to first dose)

- Review your medical history to make sure you do not have any conditions that interfere with your participation in this study.
- Have a complete physical exam, including height and weight.
- Have your vital signs (blood pressure, pulse, temperature, and respiratory rate) measured.
- Determine your functional state (known as ECOG performance status).
- Draw blood to assess your blood count, chemistry panel, LFTs, TSH, PSA, and testosterone. Another tube of blood will also be drawn for research purposes.
 - Up to approximately 2 tablespoons of blood will be taken throughout the screening process.
- Undergo CT/MRI scan and a bone scan to map your cancer and determine staging.
- Review your current medications, both prescription (e.g., medications for hypertension, diabetes, or allergies) and non-prescription (e.g., vitamins, herbal supplements, aspirin). It is very important that you tell the study doctor and staff all the medications you are currently taking.

Main treatment with pembrolizumab:

Pembrolizumab will be administered intravenously in clinic at a dose of 200 mg every 21 days. You will continue to take the drug until clinical progression or unacceptable toxicity. If you experience any side effects, your doctor will discuss various management options such as temporarily stopping pembrolizumab, directly treating the side effect, or even stopping the pembrolizumab if the side effect is severe enough. Your doctor will discuss this with you should the situation arise.

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Also, you will undergo various tests and procedures throughout the treatment period. The following table shows which main treatment procedures are standard of care (SOC) versus research.

Standard of Care	Research
Interval history and medical condition review	Pembrolizumab
Physical exam	Research blood
Vitals and ECOG	
Clinical laboratory (blood and PSA)	
Tumor assessment via CT/MRI/Bone scan	

The chart below shows the tests and procedures that will occur during the treatment period.

VISIT	WHAT HAPPENS
Main Treatment	The following procedures will be performed before you take pembrolizumab at the beginning of every cycle (21 days): - Review your interval history and report any changes in your health. - Have a complete physical exam, including height and weight. - Have your vital signs (blood pressure, pulse, temperature, and respiratory rate) measured. - Determine your ECOG performance status. - Draw blood to assess your blood count, chemistry panel, LFTs, PSA, and testosterone. Another tube of blood will also be drawn for research purposes. - Research blood will be collected at C4D1 (Cycle 4, day 1) and every three cycles thereafter. - Up to approximately 2 tablespoons of blood will be taken throughout the main treatment. - Report any changes in your medications.

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Every 12 calendar weeks	• Draw blood for thyroid (TSH) testing every 12 weeks after screening. ◦ Up to approximately 2 tablespoons of blood will be taken throughout this process. • Undergo restaging imaging (CT/MRI and bone scan) every 12 weeks after C1D1 (cycle 1, day 1) to measure your cancer.
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Treatment discontinuation:

Once you clinically progress or experience unacceptable toxicity, you will be withdrawn from the study. A set of tests will be conducted to check the status of your health and cancer.

The chart below shows the tests and procedures that will occur after discontinuation.

VISIT	WHAT HAPPENS
Treatment discontinuation (within 30 days after last dose)	• Review your interval history and report any changes in your health. • Have a complete physical exam, including height and weight. • Have your vital signs (blood pressure, pulse, temperature, and respiratory rate) measured. • Determine your ECOG performance status. • Draw blood to assess your blood count, chemistry panel, LFTs, and PSA, and testosterone. ◦ Up to approximately 2 tablespoons of blood will be taken throughout the discontinuation process. • Report any changes in your medications. • Undergo restaging imaging (CT/MRI and bone scan). Scans will not occur if your last scan either showed disease progression or occurred less than 12 weeks before treatment discontinuation.

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- Undergo a second biopsy of a metastasis. This biopsy is the same in nature and process as the biopsy you underwent prior to starting treatment to determine your genetic mutations.
 - The biopsy should be performed within 45 days of the last drug dose.
 - This biopsy will be used for correlative analyses to determine the efficacy of pembrolizumab and thus will be conducted purely for research purposes.
 - Even though you had a biopsy at baseline prior to treatment with pembrolizumab, this post-treatment biopsy is still very important because the tumor can change over time and in response to the pembrolizumab treatment.

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

If you decide to take part in this study, you will have to:

- Keep your study appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
- Report to study doctors any changes in your physical or mental condition, especially if you think these changes may be due to the study drug. This is important for your own safety and the value of the study.
- Review all your current medications and supplements with your study doctor and staff at each research visit. You must also let them know of any changes made to your medications in between visits.
- Tell the study doctor or staff if you believe you might have gotten your partner pregnant. Pembrolizumab may have adverse effects on a fetus in utero. You should not plan to conceive or father children within the projected duration of the study. Contraception must be used while on treatment with Pembrolizumab plus an additional 120 days after the last dose of Pembrolizumab. You should also refrain from donating sperm during this period.

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- Ask questions as you think of them.
- Tell the study doctor or staff if you change your mind about remaining in this study.
- While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

WHAT WILL HAPPEN TO MY BLOOD AND TUMOR TISSUE SPECIMENS?

What will happen to my samples?

As soon as specimens (i.e. blood and tissue) are collected by study personnel at your local site, your samples intended for research will be labeled with a code that does not contain any personal identifiers. The key to the code will remain locked in the research office that is only accessed by study personnel. Some of your samples, especially blood samples, will be sent for standard processing to the local VA laboratory. Some of your specimens (blood or tissue) will be sent to a commercial vendor for genetic analysis. These specimens will only be used for the tests written in this informed consent. The commercial vendor will store your tissue specimens during the testing process and then return any remaining sample back to the Department of Pathology at VA Greater Los Angeles Healthcare System (VA GLAHS) in West LA. On the other hand, blood specimens sent to a commercial vendor will be completely exhausted during analysis; any blood that may remain after testing will be destroyed and discarded.

Since this is a multisite study, all biopsy specimens collected will be sent to the coordinating site, VA GLAHS in West LA. These specimens will be coded and shipped via a VA-approved secure courier. At VA GLAHS, the specimens will be stored in Dr. Matthew Rettig's future biorepository on site for analysis. Dr. Matthew Rettig will be submitting a request to create this new biorepository. Currently, he is using his laboratory as a temporary biorepository until this new one is approved and established. Any remaining tissue sample after testing will be stored in this biorepository for future research outside this study.

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None of your specimens will be destroyed. Unused specimens will be used for future research to access clinical data indefinitely. You can request to have all of your specimens destroyed at the end of the study. If you would like to allow the research team to be able to use your left-over specimens for future research, then please check the box below:

☒ I agree to allow any of my remaining specimens to be used for future research.

There are no plans to share the results of exploratory testing performed on your specimens. These results are only for research purposes and will be neither used to make decisions about your medical care nor placed in your medical record. However, certain exploratory test results may be shared with you. If these results show genetic changes that may affect your future medical care or that of your family members, your study doctor may wish to discuss the results with you and suggest additional testing.

How will my identity be protected?

Your research blood and tumor tissue specimens will not be marked with any personal identifiers. As soon as they are collected by a study personnel, your samples will be labeled with a code. The key to the code will remain locked in the research office that is only accessed by study personnel. Only coded specimens will be sent to commercial vendor and VA GLAHS in West LA. Although your study team will make every effort to protect your identity, complete privacy cannot be guaranteed.

Will I get the results of my specimen testing?

Your study doctor will receive the results of the genetic testing and share them with you as soon as they are available. The results will give you information on the genetic mutations observed in your tumor DNA, such as mismatch repair deficiencies or inactivation of CDK12. Based on the type of information discovered, your study doctor may refer you to a genetic counselor for additional testing to see if the mutation is also seen in your blood relatives. The study doctor and/or genetic counselor will discuss how these results may impact you and your family. The results of this additional testing will be collected as part of the study.

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The study investigators will perform research testing on your tissue specimens that is independent of the genetic analysis to be performed at commercial vendor. There are no plans to share the results of other testing performed on your specimens. These results are only for research purposes and will be neither used to make decisions about your medical care nor placed in your medical record. However, certain exploratory biomarker test results may be shared with you. If these results show genetic changes that may affect your future medical care or that of your family members, your study doctor may wish to discuss the results with you and suggest additional testing.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the side effects listed. Rare, unknown, or unexpected risks also may occur. Side effects may vary from person to person and can range from mild to very severe. If you have any side effects because of taking part in this study, tell your study doctor immediately, even if you don't think they are due to the study drug.

Tumor Biopsy

A needle will be used to take multiple cores of tumor tissue from a metastatic site. The common risks of this procedure include pain at the biopsy site, discomfort, infection, bleeding, swelling, bruising, and injury to nearby organs. If severe bleeding occurs, a transfusion may be needed. However, the specific risks will depend on the biopsy site. Ask the study doctor to discuss more specific biopsy risks based on the site of your biopsy.

Image guided biopsies conducted by the Department of Radiology may use local anesthesia, such as lidocaine. The common risks of using such anesthesia include bleeding, infection, burning sensation, and pain at the site of injection. At the discretion of the attending Radiologist, patients may require conscious sedation with midazolam hydrochloride (Versed). The common side effects of Versed are headache, somnolence, and hiccups.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: October 22, 2019

LSI Approval Date: October 30, 2019

LSI Verification Date: NA



Participant Name

Date: 3/10/20

Title of Study: A Single-arm, Open-label, Phase II Study of Checkpoint Inhibitors in Men with Progressive Metastatic Castrate Resistant Prostate Cancer Characterized by a Mismatch Repair Deficiency or Biallelic CDK12 Inactivation (CHOMP)

Principal Investigator: Matthew Rettig, MD

VA Facility: VA GLAHS – West LA

Principal Investigator for Multisite Study: Matthew Rettig, MD

Blood Sampling

Having blood drawn from a vein in your body may cause some pain, redness, or bruising where the needle is inserted. An infection is also possible but rare. If you feel faint while having your blood drawn, you should sit or lie down to avoid falling.

Pembrolizumab Side Effects

The following is a list of side effects due to pembrolizumab reported by physicians and patients who have taken this study drug:

Very common (Occurring in > 10% of patients):

- Feeling tired (also known as fatigue or lethargy)
- Itchy skin (pruritus)
- Skin rash (dermatitis) will appear as changes in skin color and/or texture. Some rashes may be itchy, painful, or cause no symptoms at all. This can vary from mild to severe.
- High blood sugar (hyperglycemia)
- Low thyroid levels (hypothyroidism)
- Stomach-related effects, such as diarrhea, decreased appetite, nausea, and constipation.
- Increased liver tests such as serum alkaline phosphatase and transaminases. These changes will be evaluated in the context of other side effects and test results.
- Increased serum creatinine, a measure of kidney function.
- Increased pain in joints (arthralgia)

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Common (Occurring in 1% to 10% of patients):

- Inflammation of the heart lining (pericarditis)
- Peripheral neuropathy
- Colitis
- High bilirubin in the blood (hyperbilirubinemia)
- Muscle-related effects, such as arthritis, myalgia, and myositis
- Physical weakness or lack of energy (asthenia)
- Inflammation of the eye (uveitis)
- Acute renal failure
- Pneumonitis (inflammation of lung tissue)
- Infusion-related reactions (a type of hypersensitivity reaction that develops during or shortly after administration of a drug such as fever, pruritus (itchy skin), and chills)
- Skin discoloration in certain areas causing white patches (vitiligo)

Rare (Occurring in <1% of patients):

- Encephalitis (acute inflammation of the brain usually resulting from either viral infection or the body's own immune system mistakenly attacking brain tissue)
- Guillain-Barre syndrome, a disorder that causes muscle weakness from your body's own immune system attacking your nerves (this muscle weakness can spread to your whole body)
- Inflammation of the pituitary gland (hypophysitis) or other pituitary issues (hypopituitarism)
- Myasthenia gravis, a disorder of muscle strength
- Myelitis, inflammation of the spinal cord which can disrupt the normal responses from your brain to the rest of your body
- Myocarditis, inflammation of muscle

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- Pancreatitis, inflammation of the pancreas (this can cause upper abdominal pain, nausea, and vomiting)
- Pyrexia, fever or a raised body temperature
- Autoimmune hepatitis (the body's immune system attacks liver cells which causes inflammation of the liver)
- Pneumonia
- Adrenal Insufficiency (adrenal glands don't make enough of certain hormones)
- Hyponatremia, low sodium concentration in the blood
- Difficult or labored breathing (dyspnea)
- Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) increase
- Pericardial effusion (buildup of extra fluid in the space around the heart)
- Type I Diabetes mellitus
- Interstitial Lung Disease (scarring of the lungs)

Allergic Reactions

As with any drug, it is possible that you could have allergic reactions to the study drug, such as itchiness, skin rash, facial swelling, and a severe or sudden drop in blood pressure. A sudden drop in blood pressure could lead to shock with loss of consciousness and possible seizures, as well as death. If you have any of the above symptoms, seek medical attention right away.

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Department of Veterans Affairs

RESEARCH CONSENT FORM

Version Date: September 18, 2019

Participant Name

Date: 3/10/20

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CT, MRI, and Bone Scans

Computed tomography (CT) scans use x-ray radiation. The amount of radiation you will receive during a CT scan is small; however, the more radiation you receive over the course of your life, the more likely it is that the cells in your body may change or you may develop a new cancer. Some CT scans require you to take a "contrast solution" that is injected into your vein. It is possible that this contrast solution may cause nausea, vomiting, itchiness, or a skin rash. In rare cases, it may cause your throat to swell, making it harder to breathe. These may be signs of an allergic reaction, so please tell the study doctor right away if you have any of these side effects. You may also experience some discomfort from lying still in an enclosed space for a prolonged time.

A magnetic resonance imaging (MRI) scan may be done instead of a CT scan (e.g., in patients with allergies to the contrast solution used in a CT scan). An MRI does not use x-ray radiation, but it does take a little longer and patients sometimes must lie in a more enclosed space than with a CT scan. A contrast solution may be injected into your vein before the scan is done to help the doctor see the tumor more clearly.

A bone scan examines the structure of your bones. To see changes and your cancer in the bone, a radioactive substance, called a "tracer," is injected into your vein and accumulates in areas where the disease (e.g., tumor) is present. The amount of tracer injected into your vein during a bone scan is very small; however, the more exposure to radioactive substance you receive over the course of your life, the more likely it is that the cells in your body may change or you may develop a new cancer. You may feel some discomfort during the injection of the tracer. It is possible that the tracer may cause redness, pain or swelling at the site of the injection. These may be signs of an allergic reaction or infection, so please tell the study doctor right away if you have any of these side effects. You may also experience some discomfort from lying still in an enclosed space for a prolonged time.

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Department of Veterans Affairs

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The total radiation dose you will receive in this research study include radiation from multiple CT and bone scans. Most of these scans will be part of your standard care, and thus you would have received them anyway. **Your CTs and bone scans will expose you to radiation. The radiation dose you will receive is approximately 3.9 times that of an occupational radiation worker in the first year and 2.2 times in subsequent years. Exposure to radiation in this research study does not exceed that of our institution's standard practice for this type of cancer. Therefore, participation in this research study will NOT increase your radiation risk from these scans. No harmful health effects from this exposure are expected; however, your long-term risk will increase if additional exposures are received.**

These values are well below the levels that have been demonstrated to result in a risk of harmful effects. To give you an idea about how much radiation you will get, we will make a comparison with an everyday situation. Everyone receives a small amount of unavoidable background radiation each year from natural sources (approximately 325 mrem). Some of this radiation comes from space, some from naturally-occurring radioactive forms of water and minerals, and some from radon gas.

This radiation exposure is necessary for this research study, but it may not be essential for your medical care. You are requested to inform the study investigators if you have received x-rays or any radiological procedures, such as CAT or CT scans, fluoroscopy, cardiac catheterization, or radioactive materials, as part of your medical care or for research purposes in the past year. If you take part again in a study involving radiation in the next 12 months, you must inform the investigator of your participation in this study. Also, you must inform your treating physicians about your participation in this study.

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Risk of Overall Participation

There is a possible risk of confidentiality and privacy breach from study documents, such as the signed informed consent, test results, enrollment note and research notes.

There is always a chance that any procedure can harm you, and the procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

There is no guarantee that you will directly or personally benefit from taking part in this research study. Having your specimens collected and tested may help determine whether your tumor has a mismatch repair deficiency or inactivation of CDK12, which can identify other clinical trials and therapies that may benefit you. It is also possible that taking pembrolizumab may delay cancer progression or extend your life. On the other hand, it is possible that pembrolizumab may lead to harmful side-effects and not impact cancer progression favorably; thus, your cancer may not get better or may even get worse on the study. Moreover, the knowledge obtained from this study may help treat other patients with your condition in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You do not have to take part in this research study to receive treatment for your prostate cancer. The study doctor will discuss other treatment options, such as standard of care therapies or other clinical trials, and the risks and benefits of each option.

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HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Taking part in this study will involve collecting personal health information about you to evaluate the effectiveness of pembrolizumab. Your personal health information can neither be collected nor used without your written permission in this consent. The personal health information that may identify you may include your medical history, physical examinations, blood and tumor specimens, radiographic scans, and any other data collected or reviewed during this research study (e.g., copies of your medical records from other healthcare providers who have treated you before and after you take part in this study). This information will be protected in the following ways:

- All patient reports and clinical samples will be assigned and identified by a code comprised of letters and/or numbers.
- The log of patients' codes, names, and contact information will be kept in a locked cabinet and on password-protected computers in the research office. The cabinets and computers are only accessed by VA-trained research personnel.
- Since this study consists of 6 VA sites across the US, the data shared between sites and the Department of Veteran Affairs will be coded and sent through either a VA-approved courier or VA-encrypted email.

A US federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. The Privacy Rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Researchers covered by this regulation are required to get your authorization to use and disclose any health information that could identify you. Another US federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

By signing this form, you give permission to Dr. Matthew Rettig, MD, the study staff, and the VA Greater Los Angeles Healthcare System to allow direct access to your medical records and personal health information for research purposes.

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RESEARCH CONSENT FORM

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VA Facility: VA GLAHS – West LA

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There are times when we might have to show your records and research data to other people. For example, someone from the Department of Veteran Affairs, Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, Food and Drug Administration, US governmental agencies, and other study monitors may look at or copy portions of records that identify you. Your study records will be kept confidential, and except as required by the law, you will only be identified by your special research code. If your personal data is disclosed to a third-party entity, then all appropriate measures will be taken to protect it. However, because of the need to release information to these parties, total confidentiality cannot be guaranteed.

You have the right to access and rectify your personal data when possible.

We will include information about your study participation in your medical record. As a result, your primary care physician and other specialist who are treating you will be informed about your participation in this study. This is for your own safety. If you do not consent to this, you cannot participate in this study.

MERCK is the supplier of Pembrolizumab, the drug used for this study. To comply with safety regulations set in place by MERCK, pregnancies as well as serious adverse events (i.e. events that result in hospitalization or death) that occur while on Pembrolizumab up to 120 days after the last dose of Pembrolizumab will be reported to MERCK. Information forwarded to MERCK will not include any Protected Health Information (PHI) such as your name, social security number, phone numbers, etc.

Results of this study may be presented in meetings or publications. Your identity will not be shared in those presentations. Information about you will be combined with that of other people taking part in this study, and a report will be written based on the combined data gathered. Any talks or papers about this study will not identify you.

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

Do not sign this consent form if you do not want to allow the release of your health information. If you choose not to give permission, you cannot participate in the research study. If you choose to not sign this consent form, your medical care will not be affected.

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WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

Costs to Participants: You will not be charged for any treatments or procedures that are part of this study. The cost of testing your blood and tumor tissue specimens is funded by the Department of Veteran Affairs. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

Merck, a pharmaceutical company, will provide the study drug at no cost while you are participating in this study. Also, all procedures that are required for this research study and are not part of your regular medical care will be provided to you free of charge.

Payment Offered for Participation: You will not be paid for participating in this study. You may be reimbursed for reasonable expenses, such as traveling, lodging and meals, related to your study visits if the site is not the medical center from which you receive your standard treatment. You will need to provide receipts and other documents to the study staff to receive this reimbursement.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

Every reasonable safety measure will be used to protect your well-being. If you are injured because of taking part in this study, the VA will provide necessary medical treatment to you at no cost unless the injury is due to non-compliance with study procedures or if the research is conducted for VA under contract with an individual or non-VA institution.

All forms of medical treatment, whether routine or experimental, involve some risk of injury. In addition to known side effects described above, you may experience unknown risks or develop unexpected complications from being in this study despite all precautions. Immediate medical treatment is available to you if you are injured because of this study. Contact your study doctor to obtain appropriate medical treatment.

Depending on the circumstances underlying the cause of your injury, the costs of diagnosis and treatment may be covered by the local site. If the study doctor determines that your injury is solely due to the study drug or procedure, not ordinary care, you will not be responsible for the cost of the treatments given. No other compensation will be offered by the VA Greater Los Angeles Healthcare System for injuries related to this study.

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VA Facility: VA GLAHS – West LA

Principal Investigator for Multisite Study: Matthew Rettig, MD

By signing this form, you neither give up any legal risks nor release the VA from any liability. Emergency and ongoing medical treatment will be provided as needed. If you should have a medical concern or get hurt or sick because of taking part in this study, call:

DURING THE DAY:

Dr. Matthew Rettig, MD at 310-478-3711 ext. 44761 or Sage Pitcher, Study Coordinator, at 310-478-3711 ext. 41156.

AFTER HOURS:

Dr. Matthew Rettig, MD at 310-478-3711, Pager: 14320.

DO I HAVE TO TAKE PART IN THE STUDY?

Participation in this study is voluntary. You may stop treatment and study procedures at any time for any reason. You may also withdraw your consent from the study, at which point your participation in the study will end and the study staff will stop collecting future data. If you no longer want to use your specimens for research, tell the study doctor. The study doctor will communicate your wishes to OncoPlex and have your samples destroyed. However, the information and data collected before withdrawal can still be reviewed by the study team. Thus, both previously collected data and previously used specimens cannot be withdrawn.

Talk to your study doctor about your choices and other tests that may provide you information about genetic mutations in your tumor before deciding to have your blood and tumor specimens tested by OncoPlex.

If you decide not to take part in the study or withdraw yourself at a later day, this will not impact your present or future medical care at the VA; you will not lose any benefits to which you are otherwise entitled to. Also, you will still receive the same standard of care that you would have otherwise received. Your study doctor will assess your symptoms and discuss treatment options with you.

To withdraw your consent from this study, you must tell your study doctor in writing.

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RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

Your participation could be stopped by the study doctor without your permission for any of the following reasons:

- Your cancer progresses.
- You have a serious side effect or abnormal laboratory result that would make it unsafe for you to continue the study.
- You have a change in your medical condition that prevents you from taking the study drug or may impact your overall well-being.
- The study doctor believes that it is in your best interest to not continue the treatment.
- You have a study-related injury.
- You do not follow the study doctor's instruction.

The study may be discontinued at any time by the Investigational Review Board (IRB), National Institute of Health (NIH), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA), or other governmental agencies as part of their duties to ensure that research participants are protected.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

You have the right to ask questions about your participation in this study at any time. If you have any questions about the study, experience any problems (e.g., study-related injury, illness, or side effect), or have concerns about your participation, you may contact Dr. Matthew Rettig, MD at 310-478-3711 ext. 44761 or the study coordinator: Sage Pitcher at 310-478-3711 ext. 41156.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

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WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

During this research study, new information that becomes available about pembrolizumab may change a person's decision to stay in the study. If this happens, your study doctor will inform you of the new information in a timely manner and discuss whether you want to continue in the study. If you decide to withdraw from the study, your study doctor will arrange for your medical care to continue. If you decide to continue in the study, you will be asked to sign an updated informed consent form. Your study doctor could also decide that it is in your best interest to withdraw from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

DOES THIS STUDY INVOLVE GENETIC RESEARCH AND HOW WILL MY GENETIC INFORMATION BE PROTECTED?

This research requires whole genome sequencing using whole blood and a tumor tissue specimen obtained from a biopsy of a metastatic lesion. The sequencing is conducted to determine whether you have a mismatch repair deficiency or a biallelic inactivation of CDK12, which is a requirement to receive study treatment. Also, the sequencing can be used to identify biomarkers of resistance and sensitivity to pembrolizumab and determine its efficacy.

Federal laws and policies provide you with protection from discrimination by health insurance companies, group health plans, and most employers based on your genetic information. A federal law called the Genetic Information Nondiscrimination Act (GINA) generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information obtained from this study.
- Health insurance companies and group health plans may not use your genetic information obtained from this study when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information obtained from this study when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. It also does not prohibit discrimination based on already known genetic disease.

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PERMISSION FOR USE OF DATA AND RE-CONTACT

By signing this consent form, you give permission to the study team to use and share your information for the purposes of this research study. Federal and regulatory audits may occur after your study participation to ensure the integrity of the data and the accuracy of the information reported during the study. This means your authorization for the release of your health information will not expire for this study.

You may cancel your authorization at any time by writing to your study doctor:

Dr. Matthew Rettig, MD
11301 Wilshire Blvd.
Bldg. 500, 4E, Room 4253
Los Angeles, CA 90073

The following information explains how your medical records and research data may be used and disclosed. All information about you will be first coded before being shared with any other entity, as applicable by law. Your study doctor will keep your personal medical records and a list each patient's name linked to his code for at least 15 years.

Regulatory authorities, such as the Food and Drug Administration, as well as members of the Ethics Committee/Institutional Review Board (IRB) and employees at the study site may review your medical records to verify study procedures and/or data.

After your coded protected health information is disclosed to the study Sponsor, the results of the study may be reanalyzed later and combined with the results of other studies. These study results can be used for other research purposes including:

- Reviewing the safety and effectiveness of pembrolizumab in prostate cancer patients.
- Conducting performance reviews of the pembrolizumab.
- Evaluating other cancer products and therapies.
- Developing a better understanding of prostate cancer.
- Improving the design of future clinical trials.

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Since this is a multisite study, your information may also be shared with the coordinating site, VA GLAHS in West LA, and, if necessary, with researchers at associated sites for the purposes of data analysis. Your research information will be kept confidential. However, some data will be shared, communicated, and stored during or after this research study.

TISSUE BANKING

After all analyses are completed, all blood and tumor tissue specimens will be shipped to the VA GLAHS in West LA and stored in a biorepository on site for analysis and future research outside of this study. Even if you are a patient at another local site participating in this study, your specimens will be sent to the coordinating site for storage. Blood specimens will be completely exhausted during analysis and thus not stored; any blood that may remain after testing will be destroyed and discarded. Dr. Matthew Rettig will be submitting a request to create this new biorepository. Currently, he is using his laboratory as a temporary biorepository until this new one is approved and established.

By signing this consent, you give permission to store your blood and tumor tissue specimens indefinitely for future research in Dr. Matthew Rettig's new biorepository at the VA GLAHS in West LA. Your specimens will be further tested and analyzed in various other studies related to prostate cancer to learn more about the physiology and mechanism of metastatic castration resistant prostate cancer. Since these tests and analyses are only conducted for research purposes, neither you nor your primary care doctor will be informed of the results. These specimens will be assigned a unique code that does not contain your name, date of birth, social security number, or any other personal identifiers. Once the linkage between your personal information and specimens has been destroyed, the researchers will not be able to determine which specimens came from you. Only those part of Dr. Matthew Rettig's research team will have access to your specimens.

Your blood and tumor tissue specimens will be used in future research to further learn about the biology of metastatic castration resistant prostate cancer. The knowledge obtained from these research studies involving the use of your specimens may help us develop new interventions and therapies that could help patients like you in the future. It can also lead to the development of commercial, pharmaceutical, or diagnostic products; you do not have any right to these future interventions.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: October 22, 2019

LSI Approval Date: October 30, 2019

LSI Verification Date: NA



Participant Name: [REDACTED] Date: 3/10/20

Title of Study: A Single-arm, Open-label, Phase II Study of Checkpoint Inhibitors in Men with Progressive Metastatic Castrate Resistant Prostate Cancer Characterized by a Mismatch Repair Deficiency or Biallelic CDK12 Inactivation (CHOMP)

Principal Investigator: Matthew Rettig, MD

VA Facility: VA GLAHS – West LA

Principal Investigator for Multisite Study: Matthew Rettig, MD

RIGHTS OF HUMAN SUBJECTS IN MEDICAL EXPERIMENTS

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another as the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of any signed and dated written consent form used in relation to the experiment.
10. Be given an opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

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VA Facility: VA GLAHS – West LA

Principal Investigator for Multisite Study: Matthew Rettig, MD

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms. Matthew Rettig has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record.

I agree to participate in this research study as has been explained in this document.

[REDACTED] Participant's Name	[REDACTED] Participant's Signature	3-10-2020 Date
Matthew Rettig Name of Person Obtaining Consent	[Signature] Signature of Person Obtaining Consent	3-10-2020 Date

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PI/SC Approval Date: October 22, 2019

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