IRB NUMBER: 16-20574
IRB APPROVAL DATE: 03/10/2022
IRB EXPIRATION DATE: 08/09/2022

Subject Name: _____
DOB:____/____/ _____
UCSF MR#: _____

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO CONSENT TO BE A RESEARCH SUBJECT
(Permission for Participation in Research, For Subjects < 13 years)

PNOC 007, H3.3K27M Specific Peptide Vaccine Combined with poly-ICLC with and without PD-1 inhibition using Nivolumab for the Treatment of newly diagnosed HLA-A2 (02:01)$^+$ H3.3K27M Positive Diffuse Intrinsic Pontine Glioma (DIPG) and newly diagnosed HLA-A2 (02:01)$^+$ H3.3K27M Positive Gliomas

If you are a parent or legal guardian of a child who may take part in this study, permission from you and the Assent (agreement) of your child may be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

This is a clinical trial, a type of research study. The study doctor, Dr. Sabine Mueller, and her associates from the UCSF Benioff Children's Hospitals, San Francisco and Oakland and the Department of Pediatric Hematology/Oncology will explain this study to you and your child. If you have any questions, you may ask the study doctor.

Clinical trials include only people who choose to take part. Please take your time to make your decision about allowing your child to participate. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

We are asking if you want to allow your child to participate in this study because your child has been newly diagnosed with a type of brain cancer called a diffuse intrinsic pontine glioma (DIPG) or another type of glioma. Your child also has a specific type of marker found on their cells called HLA-A2 (02:01) $^+$ and a specific mutation in their tumor called H3.3K27M for which we want to treat with a new drug.

Why is this study being done?

The purpose of this study is to test the safety of an H3.3K27M specific peptide vaccine (K27M/TT), in combination with a drug called poly-ICLC with or without another drug - nivolumab, in children and young adults with your child's type of brain tumor. We want to find out what effects, good and/or bad, it has on your child and their type of brain tumor.

There are three different groups in this study. Participants will be assigned to a Group based on your child's prior diagnosis. The Groups in the study are described below:

Group A: Participants in Group A consists of HLA-A2 (02:01)+, positive newly diagnosed subjects with H3.3K27M positive DIPG and will receive a vaccination with K27M/TT and an intramuscular (IM) injection of poly-ICLC.

Group B: Participants in Group B consists of other HLA-A2 (02:01)+, positive newly diagnosed subjects with H3.3K27M positive midline gliomas, including spinal cord tumors, that are not classified as DIPG and will receive a vaccination with K27M/TT and a intramuscular (IM) injection of poly-ICLC.

Group C: Participants in Group C consists of other HLA-A2 (02:01)+, positive newly diagnosed subjects with H3.3K27M positive DIPG and other midline gliomas, excluding spinal cord tumors and will receive a vaccination with K27M/TT, a intramuscular (IM) injection of poly-ICLC and an intravenous infusion of Nivolumab.

Enrollment has been completed for Groups A and B. Going forward, we will only enroll onto Group C.

The H3.3K27M specific peptide vaccine is designed to attack your child's tumor cells. The poly- ICLC will help boost your child's immune system.

Nivolumab is designed to target a specific marker on your child's cells. It is believed that when the marker is targeted, your child's immune system works better to attack tumor cells.

The H3.3K27M and poly-ICLC vaccine combination with or without nivolumab is considered experimental, because it is not approved by the Food and Drug Administration (FDA).

Polypeptide, Inc., the makers of the H3.3K27M peptide vaccine, is supplying the vaccine. Oncovir, Inc. is supplying poly-ICLC, and Seppic is providing Montanide ISA, that are part of the helper peptide. Bristol-Meyers Squibb (BMS), Inc, the makers of Nivolumab, is supplying the drug. The V Foundation, The Prasad Foundation, and BMS, Inc. are providing support to conduct this study.

Study location:
Most of the study procedures can occur at any facility. The administration of the vaccine and nivolumab needs to occur at the UCSF Benioff Children's Hospital in San Francisco or Oakland campuses.

How many people will take part in this study?

Up to 49 subjects are expected to participate in this feasibility study. About 12 subjects will participate at UCSF Benioff Children's Hospitals, San Francisco and Oakland campuses.

What will happen if you allow your child to take part in this research study?

Before you begin the main part of the study...
In order to take part in this clinical study, doctors must make sure your child has the right type of mutation in their tumor by performing a test. The tests will look for a mutation in a specific gene called H3F3A in their tumor that will be or was collected as part of standard of care. The specific test is called sequencing. If your child's tumor shows that it has the H3.3K27M mutation in the H3F3A gene, your child may be eligible to participate in the main part of this study. If the test shows your child does not have the specific mutation, your child will not be able to take part in this study. If your child is not eligible, your study doctor will discuss other treatment options with you. Doctors will also look to see if your child has a certain type of marker on their cells. Doctors will do a test on your child's blood that was collected as part of standard of care. The marker is called HLA-A2 (02:01). If your child has this type of marker, your child may be eligible to participate in the main part of this study. If tests show your child does not have the HLA-A2 (02:01) marker, your child will not be able to take part in this study.

If your child has already had this test performed on their tumor by another doctor, they may not have to repeat it. Please let your study doctor know if your child has already had this test.

In order to have the test done, doctors will need to take a piece of your child's tumor. The surgery or biopsy is part of your child's routine care. If your child has already had a prior surgery or biopsy to remove a piece of their tumor to diagnose their disease, your doctors may use this tissue and your child will not need to have another tumor biopsy. If your child's doctor recommends a standard of care biopsy, and additional tissue is being collected as part of your child's clinical care, we will use this tissue in this research study at that time.

After your child has been screened for the H3.3K27M mutation, your child will need to have the following exams, tests or procedures, within 14 days prior to enrollment, to find out if they can be in the main part of the study. These exams, tests or procedures are part of regular cancer care and may be done even if your child does not join the study. Your child will also have some procedures that are only being done because your child is in the study. These are called research procedures. If your child has had some of these exams, tests or procedures recently, they may not need to be repeated. This will be up to your study doctor.

<u>Eligibility Screening</u>
- Complete medical history including your history of prior treatments.
- Review of what medications your child is taking
- Assessment of your child's ability to perform everyday tasks
- Blood draw (about two teaspoons) for routine safety tests
- Urine analysis (**Group C, only)**
- Serum or urine pregnancy test – if your child is a female of childbearing age
- Pulse oximetry (**Group C, only**)

- MRI of brain
    - An MRI scan takes an image of your child's head or body to observe the location and size of their tumor. For the MRI scan, your child may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in their body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to your child in their arm through an intravenous catheter (a tiny tube inserted into a vein). Your child will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. Your child will lie there quietly for about one hour, during which time they will hear a loud machine-like noise. The MRI scan is done in the radiology department and takes approximately an hour and a half to complete.
    - Your child may need conscious sedation, which is a combination of medicines to help your child relax (a sedative) and to block pain (an anesthetic) during your child's MRI. Conscious sedation lets your child recover quickly and return to their everyday activities soon after their procedure. Your child will receive the medicine through an intravenous line (IV, in a vein). Your child will begin to feel drowsy and relaxed very quickly. If your child's doctor gives you the medicine to swallow, they will feel the effects after about 30 to 60 minutes.
    - If your child needs it, general anesthesia medication may also be given to him/her, to make your child sleep during the procedure. Your child will receive medication either through an IV, or your child may be given a gas that he/she will breathe from a mask. Someone from the anesthesia care team monitors your child continuously while he/she sleeps.
- MRI of spine (if clinically indicated) – MRI of spine will match brain MRI schedule

OPTIONAL CONSENT

Leftover tissue for future research:

Tissue, when available, will be collected at screening if a surgical procedure is performed as part of routine care.

After all of the tests for routine care are complete, and if there is any leftover tissue that would normally be discarded, we would like to keep it for future research. Future research may include testing related to immunologic markers related to pediatric brain tumors.

Donating your child's tissue for future research is completely voluntary. If you agree, you will be asked to complete the optional consent section of this form. More information can be found under the ***About Using Blood and Tissue for Future Research*** section on page 22 of this consent form.

During the main part of the study...

If the Eligibility Screening exams, tests and procedures show that your child can be in the main part of the study, and you choose to take part, then you will also need the following Baseline tests and procedures. They are part of regular cancer care. All subjects will receive the peptide vaccine and a helper peptide called K27M/TT with poly-ICLC every three weeks. Participants in Group C will also

receive nivolumab. The peptide vaccine is given by a shot just under the skin. The poly-ICLC is given by a shot into the muscle. Nivolumab is given by IV. All subjects will participate in the same Baseline tests and procedures unless otherwise noted below. If your child has had some of these tests done recently, they may not need to be repeated.

Day -14 (*prior to vaccinations)*

- Quality of life questionnaires, computerized cognitive assessments and survey collection (Group C, only):
    - We will collect information about your child's overall quality of life and behavioral changes by having you and your child complete questionnaires and surveys. These will be done in clinic.

Week 0, Day 1

Baseline Observations (prior to vaccination*) (All Groups, unless otherwise noted)*

- Physical and neurological exam
- Vital signs
- Assessment of your child's ability to perform everyday tasks
- Assessment of your baseline symptoms and any side effects you have from your prior treatment
- Review of what medications your child is taking
- Blood draw (about two teaspoons) for routine safety tests
- Serum or urine pregnancy test – if your child is a female of childbearing age
- Blood draw (about four tablespoons) for immune monitoring and analysis of circulating tumor DNA (week 0 only, then every 12 weeks as below)
- Pulse oximetry (**Group C, only**)
- Urine analysis (**Group C, only)**

Treatment/Vaccinations
After your child's baseline observations, your child will receive the following treatment based on which Group your child is assigned:

- **Groups A or B:**
    - Your child will receive a vaccination with K27M/TT
    - Your child will receive an intramuscular (IM) injection of poly-ICLC
- **Group C**
    - Your child will receive a vaccination with K27M/TT
    - Your child will receive an intramuscular (IM) injection of poly-ICLC
    - Your child will receive an intravenous infusion of Nivolumab. Your child's infusion can occur before or after your child's vaccinations.

Your child will be closely observed for any side-effects for at least 20 minutes following each vaccination. Please tell your study doctor or study team member at any time, if your child experiences any side-effects.

Every three weeks, Day *1 (weeks 3, 6, 9, 12, 15, 18, 21)* (*All Groups, unless noted otherwise*)

- Physical and neurological exam
- Vital signs
- Review of any side effects your child may be experiencing
- Assessment of your child's ability to perform everyday tasks
- Review of what medications your child is taking
- Blood draw (about two teaspoons) for routine safety tests
- Serum or urine pregnancy test – if your child is a female of childbearing age
- Pulse oximetry (**Group C, only**)
- Urine analysis (**Group C, only)**
- ECHO and ECG, as clinically indicated (**Group C, only**)

Treatment/Vaccinations

- **Groups A or B:**
  - Your child will receive a vaccination with K27M/TT
  - Your child will receive an intramuscular (IM) injection of poly-ICLC
- **Group C**
  - Your child will receive a vaccination with K27M/TT
  - Your child will receive an intramuscular (IM) injection of poly-ICLC
  - Your child will receive an intravenous infusion of Nivolumab. Your child's infusion can occur before or after your child's vaccinations.

Every twelve weeks, Day 1 (*weeks* 12, 24, 36, 48, 60, 72, 84, 96) (*All Groups, unless noted otherwise*)

- Brain MRI
- Spine MRI, if clinically indicated
- Blood draw (about four tablespoons) for immune monitoring and analysis of circulating tumor DNA
- Quality of Life Questionnaires and survey collection **(Group C, only)**

Week 18, Day 1 *(All Groups, unless noted otherwise)*

- Blood draw (about four tablespoons) for immune monitoring

Week 24, Day 1 *(All Groups, unless noted otherwise)*

- Physical and neurological exam
- Vital signs

- Assessment of your child's ability to perform everyday tasks
- Review of what medications your child is taking
- Review of any side effects your child may be experiencing
- Blood draw (about two teaspoons) for routine safety tests
- Serum or urine pregnancy test – if your child is a female of childbearing age
- Pulse oximetry (**Group C, only**)
- Urine analysis (**Group C, only)**
- ECHO and ECG, as clinically indicated (**Group C, only**)

Treatment/Vaccinations

- **Groups A or B:**
  - Your child will receive a vaccination with K27M/TT
  - Your child will receive an intramuscular (IM) injection of poly-ICLC
- **Group C**
  - Your child will receive an intravenous infusion of Nivolumab.

If the study doctor thinks your child is responding well to the treatment, your child will continue to get nivolumab every 3 weeks, and the vaccine every 6 weeks (at the same time as nivolumab) beginning at week 27, for up to 96 weeks (about 2 years total).

Every three weeks, Day 1 (weeks 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96)) (All Groups, unless otherwise noted)

- Physical and neurological exam
- Vital signs
- Review of any side effects you may be experiencing
- Assessment of your ability to perform everyday tasks
- Review of what medications you are taking
- Blood draw (about two teaspoons) for routine safety tests
- Serum or urine pregnancy test for females of childbearing age
- Pulse oximetry (**Group C, only**)
- Urine analysis (**Group C, only**)
- ECHO and ECG, as clinically indicated (**Group C, only**)

Treatment/Vaccinations

- **Groups A or B:**
  - Your child will receive a vaccination with K27M/TT
  - Your child will receive an intramuscular (IM) injection of poly-ICLC
- **Group C – Vaccine and poly-ICLC will only be given every 6 weeks (starting with week 27), and Nivolumab *every 3 weeks***
  - Your child will receive an intravenous infusion of Nivolumab, *every 3 weeks*. Their infusion can occur before or after their vaccinations, if they are receiving vaccine this day
  - Your child will receive a vaccination with K27M/TT

- Your child will receive an intramuscular (IM) injection of poly-ICLC

Your child will be closely observed for any side-effects for at least 20 minutes following each vaccination. Please tell your study doctor or study team member at any time, if your child experience any side-effects.

Every 3 months and 6 months for two years. After two years, you and your child will complete the questionnaires every 3 months and 12 months while they are on treatment (Group C, only)

- Quality of Life Questionnaires and survey collection

End of Treatment Visit *(on the last day of treatment if not assessed within 14 days before) (All Groups, unless otherwise noted)*

- Evaluation of your clinical response
- Brain MRI (if not done within 30 days prior)
- Spine MRI (if clinically indicated and if not done within 30 days prior)
- Physical and neurological exam
- Vital signs
- Review of any side effects you may be experiencing
- Assessment of your ability to perform everyday tasks
- Review of what medications you are taking
- Blood draw (about two teaspoons) for routine safety tests
- Serum or urine pregnancy test for females of childbearing age (if last day of treatment)
- Pulse oximetry **(Group C, only)**
- Urine analysis **(Group C, only)**
- ECHO and ECG, as clinically indicated **(Group C, only)**
- Quality of Life Questionnaires and survey collection **(Group C, only)**

Treatment/Vaccinations (if last day of treatment)

- **Groups A or B:**
  - Your child will receive a vaccination with K27M/TT
  - Your child will receive a intramuscular (IM) injection of poly-ICLC
- **Group C**
  - Your child will receive an intravenous infusion of Nivolumab. The infusion can occur before or after their vaccinations.
  - If it's been 6 weeks from your child's last vaccine, they will receive a vaccination with K27M/TT
  - Your child will receive a intramuscular (IM) injection of poly-ICLC

When your child is finished receiving K27M/TT peptide vaccine…

Around 30 days after your child's last day of treatment, the study team will check in with you for an

evaluation of any adverse events and to review any medications your child is taking. This may be done in the clinic or over the phone. We will continue to follow up every three months for two years by chart review and/or telephone contact, unless you/your child decide not to participate. During the follow up period, we will collect information about your child's disease status and whether they have started any new treatment. If your child is in Group C, we will collect quality of life questionnaires and surveys to assess and grade your child's brain function every 12 months for 24 months. If your child goes go on to receive new anti-cancer therapy, you and your child will no longer need to complete the questionnaires, surveys and assessments.

OPTIONAL CONSENT

Leftover blood for future research:

Research blood will be collected before (day 1, week 0) and during (day 1, every 12 weeks and week 18) study treatment.

After all of the tests for this research are complete, and if there is any leftover research blood, we would like to keep it for future research. Future research may include testing for immunologic markers and circulating tumor DNA related to brain tumors.

Donating your child's blood for future research is completely voluntary. If you agree, you will be asked to complete the optional consent section of this form. More information can be found under the ***About Using Blood and Tissue for Future Research*** section on page 22 of this consent form.

How long will your child be in the study?

Your child may continue the treatment for up to about two years (24 months). Your child will receive the peptide vaccine and nivolumab every three weeks for about six months, and if the doctor thinks your child is responding well, they will continue receiving nivolumab every three weeks and the vaccine peptide every six weeks for a total of about two years as long as he/she does not have severe side effects, unless you decide to withdraw your child's consent to participate in this study, or the study is closed.

Can my child stop being in the study?

Yes. You and/or your child can decide to stop at any time. Tell the study doctor if you and/or your child are thinking about stopping or decide to stop. She/he will tell you how to stop your child's participation safely. The study doctor may ask to do some end-of-study tests.

It is important to tell the study doctor if you are thinking about stopping so any risks related to the study can be evaluated by the study doctor. Another reason to tell the doctor that you are thinking about stopping is to discuss the follow-up care and which testing could be most helpful for your child.

The study doctor may stop your child from taking part in this study at any time or for any reason if she/he believes it is in your best child's interest, if you and/or your child do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

Your child may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give your child medicines to help lessen side effects. In some cases, side effects can be serious including death, long lasting, or may never go away.

You should talk to the study doctor about any side effects your child experiences while taking part in the study.

The K27M/TT vaccine has not been given by itself. The side effects listed are when the combination of the study drug K27M/TT vaccine with poly-ICLC and Montanide is given. As of 12/31/2019, 29 patients have been treated on this trial.

Risks and side effects related to the study drug K27M/TT vaccine in combination with poly-ICLC and Montanide:

Likely (>10%)

- Mild inflammatory reaction at the site where the vaccine is given
- Development of a hard area of skin at the site of injection that may last for months*
- Temporary pain at the site of injection.
- Hypersensitivity- which means you might get an allergic reaction to something in the vaccine combination
- Vomiting
- Feeling tired
- Elevation of liver enzymes that may indicate liver damage.
- White blood cell count decreased, which may increase risk of infection
- Nausea
- Difficulty walking
- Flu like symptoms, such as chills, fever, and headache
- Fever
- Red blood cell decreased, which may increase need for transfusion

**Your treating team can use an area of skin nearby the vaccine site to try to minimize any problems.*

Less Likely (5-10%)

- An abnormal sensation in the skin
- Diarrhea
- Neutrophil count decreased, which may increase risk of infection
- Weight loss
- Loss of appetite
- Low potassium in your blood
- Partial vision loss
- Pain on swallowing
- Neutrophils increased, which may indicate stress or infection
- Increased non-fasting blood sugar levels in your blood
- Blood urea nitrogen increased, which may indicate kidney injury
- Low phosphate in the blood
- Joint pain
- Muscle weakness
- Muscle pain
- Pain
- Allergic reaction
- Bruising
- Creatinine increased, which may indicate kidney injury
- Itchiness
- Platelet count decreased or platelet volume decreased, which may increase risk of bleeding or bruising

Rare and Serious

- Pneumonia, an infection in the lung. One (1) patient experienced this while on the trial.
- Meningitis, a possible infection or inflammation of the lining of the brain and spine. One (1) patient experienced this while on the trial.
- Pseudo progression of tumor:
  There is a slight chance that because of this treatment it may be hard to distinguish true tumor progression from the changes caused by the treatment, even with repeated MRI scans. "Pseudo-progression" is caused by inflammation in the brain caused directly by the immune response. Both true tumor growth and pseudo-progression may cause swelling in the brain, and both may cause similar symptoms, such as headache and worsening of neurological signs, including weakness, numbness, and balance problems (among others, depending on where the tumor is located). Treatment is not always needed, but if required, medications such as dexamethasone (a steroid) may be given to reduce the symptoms. In some cases, a biopsy may be suggested to confirm either true tumor growth or pseudo-progression.

Studies using poly-ICLC as a single agent therapy have shown the following side effects:

Likely (>10%)

- Pain at injection site
- Feeling tired
- Flu like symptoms
- Low white blood cells, which may increase risk of infection.
- Low platelet count, which may cause bleeding and bruising.
- Low number of red blood cells, which helps carry oxygen.

Less Likely (5-10%)

- Elevation of liver enzymes that may indicate liver damage.

Rare, but Serious (<5%)

- Diarrhea
- Swelling around the brain tumor.

Discomforts and risks seen with the use of nivolumab alone

Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. In patients under 18 years of age, computer models have shown that these patients may have higher levels of nivolumab in the blood compared to adults. This may increase the risk of side effects. You should tell your child's doctor or nurse right away about any possible side effects your child experiences.

Very Common (Occurs in more than 10 out of 100 patients):

- Abdominal pain
- Cold symptoms such as stuffy nose, sneezing, sore throat
- Constipation
- Cough, shortness of breath
- Decrease in appetite
- Hand-foot syndrome due to cytotoxic therapy, which may cause redness, pain, or peeling of palms and soles
- High blood pressure
- High blood glucose
- Itchy skin or rash
- Nausea
- Numbness, pain, and tingling of the arms, legs, fingers, and/or toes
- Pain – can include abdominal, joint, muscle, and/or head pain
- Sores in mouth, which may cause difficulty swallowing
- Tiredness (fatigue)
- Vomiting

Very common, but serious (Occurs in more than 10 out of 100 patients):

- Damage to intestinal tract
- Damage to liver, which may cause yellowing of the eyes and skin
- Damage to the lungs, which may cause shortness of breath
- Diarrhea
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- Infection of urinary tract
- Tiredness and low blood pressure, which may cause feeling faint (Adrenal Insufficiency)

Occasional, but serious (Occurs in at least 1 out of 100 patients):

- Anemia, kidney problems, which may cause tiredness, bruising, swelling, or may require dialysis
- Damage to bone marrow
- Damage to eye
- Damage to joints and muscles
- Damage to lymph nodes
- Damage to kidneys
- Damage to pancreas
- Damage to vessels
- Fluid around lungs, which may cause shortness of breath
- Guillain-Barre Syndrome, which may cause numbness and tingling of the arms, legs, and upper body, paralysis or shortness of breath
- Heart failure or damage to the heart, which may cause shortness of breadth, swelling of ankles, and tiredness
- Internal bleeding, which may cause belly pain, black tarry stool, and blood in vomit
- Low platelets, which may cause bruising, bleeding
- Pain in belly
- Severe blood infection
- Severe skin rash with blisters and peeling, which can involve mouth and other parts of the body (SJS-Stevens Johnson Syndrome; TEN-Toxic Epidermal Necrolysis)
- Shortness of breath (sarcoidosis)
- Swelling of body parts (eye, inner ear, lining of the brain, skin and changes in hair or hair loss)
- Swelling or redness of the skin
- Swelling of brain
- Tear or a hole in the bowels, which may cause pain or that may require surgery
- Viral infection

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the

tissues of the lung. This adverse effect has been reported in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non- invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse <u>AT ONCE</u> if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

- Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal. There might be additional unknown risks.

Complications, including fatal events, have occurred in patients who received allogeneic hematopoetic stem cell transplantation (HSCT) before or after nivolumab.

Complications, including rejection, have also been reported in patients who have received an organ or tissue transplant. Treatment with nivolumab may increase the risk of rejection of the organ or tissue transplant.

<u>There may be additional side effects related to the study treatment that your treating team still does not know. It is very important to tell them if your child has any bad experiences while on this study.</u>

Other risks related to study procedures:

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, fainting, and infection.

Study Drug Combination: The side effects of the combination of poly-ICLC and K27M/TT vaccines with nivolumab are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects your child experiences while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects.

Risk of inadequate specimens for diagnostic purposes: Providing parts of your surgically-removed tissue for research could, in rare cases, result in too little tissue being available for your doctors to make a clinical diagnosis (or complete other clinically important tests). To minimize this risk, a Pathologist (or a pathology designee) carefully evaluates every tissue specimen at the time of surgery to decide if it can safely be provided for research. With this process in place, we believe the risk of negatively impacting your clinical care through providing tissue for research is extremely small (below 1%).

MRI risks: Because the MRI machine acts like a large magnet, it could move iron- containing objects in the MRI room during the examination, which in the process could possibly harm your child. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If your child has a piece of metal in his/her body, such as a fragment in the eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, your child will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for your child. In particular, he/she may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why your child will be asked to wear ear plugs. At times during the test, your child may be asked to not swallow for a while, which can be uncomfortable. Your child may require conscious sedation or general anesthesia for the MRI if he/she is not able to sit still in the scanner. Please see risks related to general anesthesia and conscious sedation risks below.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), subjects are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Subjects with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in subjects with normal kidney function. Before your child has a MRI scan requiring an injection of gadolinium contrast, he/she will have a blood test in order to check the function of his/her kidneys. Based on your

child's medical history and the results of the test, a doctor will decide whether it is safe for your child to undergo the MRI scans.

Echocardiogram: This examination uses sound waves to make pictures of your child's heart, which helps determine how well their heart squeezes blood. He/She will be asked to lie on their left side while a technician places a probe with gel on their chest to create images of their heart to determine the function and size. The procedure is done in the cardiology department and will take approximately 45-60 minutes. The cardiac echogram might cause your child to be uncomfortable from the pressure of the probe on your child's chest or lying still for the examination

Electrocardiogram (ECG) risks: The ECG involves placing electrodes on the skin. Your child may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

Risks related to general anesthesia: General anesthesia given for an MRI may cause your child to wake up tired. Your child may also feel sick to the stomach, and have a dry mouth, sore throat, or feel cold or restless until the effect of the anesthesia wears off. Sometimes, nausea and vomiting can be treated with other medicines. Although it is rarely needed, a tube may be inserted into your child's windpipe to help him/her breathe if he/she should have difficulty breathing. This tube may cause a sore throat. In very rare circumstances, general anesthesia can be associated with hepatitis from the anesthetic medication, or death from complications of the anesthesia.

Conscious sedation risks: If sedation medication is given for an MRI scan, it will be given through an IV or by mouth. Your child may feel pain from the initial needle stick. Possible bruising from where the needle went into the skin may occur, as well as rarely, an allergic reaction to the medication. Vomiting or inhaling food contents from the stomach are also risks of sedation. These risks are minimized if your child does not eat for a minimum of 6-8 hours prior to any procedure.

Confidentiality risks: There is a risk someone could get access to the personal information in your child's medical records or other information researchers have kept about your child. Someone might be able to trace this information back to you or your child. The researchers believe the chance that someone will identify your child is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for your child to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researcher believes the chance these things will happen is very small, but cannot promise that they will not occur. Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your child's health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your child's medical record.

Reproductive risks: Your child should not become pregnant or father a baby while on this study because we are not sure how the drugs in this study might affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that your child needs to use birth

control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child carried by a woman who takes part in this study. Therefore, all women who can become pregnant and are sexually active, or their sexual partners, must use birth control measures while in this study and for 30 days after the last administration of the peptide vaccine. The following birth control measures are acceptable:

- Intrauterine device (IUD),
- Birth control pills,
- Barrier device.

Females of childbearing potential must have a pregnancy test before taking part in this study. For the pregnancy test, your child will give a blood sample taken from a vein in your arm with a needle 7 days before the study. Your child may also submit a urine sample. Your child will be told the results of the pregnancy test. If the pregnancy test is positive, your child will not be able to take part in the study

Genetic Testing Risks: Genetic information (also known as genotype data) and the medical record data (also known as phenotype data) may be shared broadly in a coded form for future genetic research or analysis. We may give certain medical information about your child (for example, diagnosis, blood pressure, age if less than 85) to other scientists or companies not at UCSF, including to a (public or controlled access) government health research database, but we will not give them your child's name, address, phone number, or any other identifiable information. Research results from these studies will not be returned to you or your child except as previously described for study eligibility purposes.

Donating data may involve a loss of privacy, but information about your child will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Genetic information that results from this study might not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your child's health. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. It is possible that future research could one day help people of the same race, ethnicity, or sex as your child.
However, it is also possible through these kinds of studies that genetic traits might come to be associated with your child's group. In some cases, this could reinforce harmful stereotypes.

There will be no direct benefit to your child from allowing your data to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease. If the data or any new products, tests or discoveries that result from this research have potential commercial value, your child will not share in any financial benefits. If you or your child decide later that you do not want your information to be used for future research, you can notify the investigator in writing [redacted] and any remaining data will be destroyed. However, we cannot retract any data has been shared with other researchers.

Neurocognitive Testing Risks: The computerized neurocognitive testing may cause embarrassment

and/or frustration. You or your child may choose to stop the test at any time.

Unknown Risks: The treatment may have side effects that no one knows about. The researchers will let you and your child know if they learn anything that might make you change your mind about allowing your child to participate in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your child's health better. While doctors hope K27M peptide vaccine with or without nivolumab will be more useful against cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about K27M peptide vaccine with or without nivolumab as a treatment for cancer. This information could help future cancer subjects.

What other choices do we have if I do not allow my child to take part in this study?

Taking part in this research study is voluntary. Instead of being in this research study, you and your child have other options, which include:

- Getting treatment or care for your child's cancer without being in a study. You may have alternative treatment options such as brain surgery, radiation therapy, and chemotherapy to treat your child's brain tumor.
- Taking part in another type of research study.
- Not participating in the study.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how your child feels. Comfort care tries to keep your child as active and comfortable as possible

Please talk to the study doctor about your choices before deciding if you will allow your child to take part in this study.

Will my child's medical information be kept private?

We will do our best to make sure that the personal information in your child's medical record is kept private. However, we cannot guarantee total privacy. Your child's personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your child's name and other personal information will not be used.
Organizations that may look at and/or copy your child's medical records for research, quality assurance, and data analysis include:

- The University of California
- Members of the Pacific Pediatric Neuro Oncology Consortium (PNOC)
- The National Cancer Institute (NCI), the Food and Drug Administration (FDA) and other government agencies involved in overseeing research.
- Bristol Meyers Squibb, Inc.
- Polypeptide Inc.
- Oncovir, Inc.
- Seppic, Inc.

Participation in research may involve a loss of privacy, but information about you and your child will be handled as confidentially as possible. If your child does not have a UCSF Benioff Children's Hospital, San Francisco or Oakland medical record, one will be created for them. Your consent form and some of your child's research test results will be included in this record. Therefore, people involved with your child's future care and insurance may become aware of their participation and of any information added to your child's medical record as a result of their participation. Study tests that are performed by research laboratories and information gathered directly from your child by the researchers will be part of your child's research records but will not be added to your child's medical record. Your child's personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your child's name and other personal information will not be used. Hospital regulations require that all health care providers treat information in medical records confidentially.

What are the costs of taking part in this study?

Polypeptide Inc., the makers of the H3.3K27M peptide vaccine, is supplying the vaccine at no cost to you. Oncovir, Inc. is supplying the poly-ICLC, and Seppic is supplying Montanide ISA, that are a part of the helper peptide free of charge. Bristol-Meyers Squibb (BMS), Inc, the makers of Nivolumab, is supplying the drug. The V Foundation, The Prasad Foundation, and BMS, Inc. are providing support to conduct this study.

Some of the services your child will receive are being done only because your child is participating in this research study. Examples of these 'research only' services include: review of

side effects, immune monitoring, some blood collections/tests, etc. Those services will be paid for by the study and will not be billed to you or your health insurance company. If you believe you have received a bill for a research related procedure contact the study team and the UCSF Medical Center office that sent the bill.

In addition, some of the services your child will receive during this research study are considered to be "routine clinical services" that you would have received even if you were not participating in the research study. Examples are physical exams and some tumor imaging. These services will be billed to your health insurance company, and you will be responsible for paying any deductibles, co-payments or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

If you have any questions, your child's doctor and the study team will be able to provide you with answers.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call **1-800-4-CANCER (1-800-422-6237)** and ask them to send you a free copy.

Will I be paid for taking part in this study?

You will not be paid for allowing your child to take part in this study.

What happens if my child is injured because he/she takes part in this study?

It is important that you tell the study doctor Dr. Sabine Mueller, if you feel that your child has been injured because of taking part in this study. You can tell the doctor in person or call her [redacted]

Treatment and Compensation for Injury: If your child is injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415-476-1814.

What are my child's rights if he/she takes part in this study?
Allowing your child to take part in this study is your choice. You may choose either to allow your child to take part or not to take part in the study. If you decide to allow your child to take part in this study, he/she may leave the study at any time. No matter what decision you make, there will be no penalty to you or your child and you will not lose any of your regular benefits. Leaving the study will not affect your child's medical care. Your child can still get his/her medical care from our institution.

We will tell you about new information or changes in the study that may affect your child's health or your willingness to allow your child to continue to participate in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

For questions about the study, research related problems, or if you think your child has been injured, contact the study doctor, Dr. Sabine Mueller [redacted].
If you wish to ask questions about the study or your child's rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476- 1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by

U.S. Law. This Web site will not include information that can identify you or your child. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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ABOUT USING BLOOD AND TISSUE FOR RESEARCH

Your child will have fresh or archived tissue collected as part of the screening procedures to test for the H3.K27M mutation, and blood collected as part of their participation in this clinical trial at day 1 (week 0), day 1 every 12 weeks, and day 1 (week 18) for immune monitoring and analysis of circulating tumor. After the study has been completed, instead of discarding your child's leftover specimens, with your permission, we will save (bank) them for possible future research to learn more about cancer and other diseases. Any leftover blood and tissue samples will be coded and stored indefinitely at the University of California, San Francisco. Only Dr. Mueller and her associates at the University of California will be able to identify the samples.

The research that may be done with your child's tissue blood is not designed specifically to help your child. It might help people who have cancer and other diseases in the future.

Reports about research done with your child's blood and tissue will not be given to you or your doctor. These reports will not be put in your child's health record. The research will not have an effect on your child's care. If the research is published or presented at scientific meetings, your child's name and other personal information will not be used.

Things to Think About

If you decide now that your child's tissue and blood can be collected for research, you can change your mind at any time. Just contact the study doctor, Dr. Sabine Mueller at the University of California San Francisco (UCSF), [redacted] and let us know that you do not want us to use your child's blood and tissue. Then any tissue that remains will no longer be used for research. We will destroy any remaining identifiable specimens and information if they are no longer needed for your child's care. However, if any research has already been done using portions of your child's specimens, the data will be kept and analyzed as part of those research studies.

In the future, people who do research may need to know more about your child's health. While the study doctor may give them reports about your child's health, she will not give them your child's name, address, phone number, or any other information that will let the researchers know who you or your child are.

Your child's blood and tissue will be used only for research and will not be sold. The research done with your child's tissue may help to develop new products in the future. You will not receive any payment or financial benefit from any products, tests, or discoveries derived from these samples.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other

diseases, how to prevent them, and how to treat them.

Risks

- The greatest risk to you and your child is the release of information from your child's health records. We will do our best to make sure that your child's personal information will be kept private. The chance that this information will be given to someone else is very small.

  Confidentiality: Donating specimens may involve a loss of privacy, but information about you and your child will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Your child's name will not be used in any published reports from research performed using his/her specimens. The manager of the tissue bank and select tissue bank staff members will have access to information about your child, but they will not release any identifying information about your child to researchers using your child's specimens.

  In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genome-wide studies. The NIH and other data banks may store your genetic information and give it to other qualified researchers to do more studies. Qualified researchers that can access the national databases can be from the government, academic, or commercial institutions. We do not think that there will be further risks to your privacy and confidentiality by sharing your genome-wide analysis with these databanks; however, we cannot predict how genetic information will be used in the future. The genetic information from the specimens (also known as genotype data) and the medical record data (also known as phenotype data) will be sent with only a coded number attached. Your name and other identifiable information will never be given to them.

  There are many safeguards in place to protect your information while it is stored in repositories and used for research.

Making Your Choice

Please think about your choice. After reading, put your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415- 476-1814.

The choice to let us keep any leftover blood and tissue specimen for future research is optional and is up to you. No matter what you decide to do, it will not affect your child's care.

1. I allow my child's leftover tissue to be kept for use in future research about pediatric brain cancer:

YES	*NO*

2. I allow my child's leftover blood specimen to be kept for use in future research about pediatric brain cancer:

YES	*NO*

CONSENT

You have been given signed and dated copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Print name of participant: _____

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Person Obtaining Consent

_____ _____
Date Witness Signature
(Only required if the participant is a non-English speaker)

The person being considered for this study is unable to consent for himself/herself because s/he is a minor. By signing below, you are giving your permission for your child to be included in this study.

_____
Parent or Legal Guardian Date

Medications to Avoid

***PNOC 007,* H3.3K27M Specific Peptide Vaccine Combined with poly-ICLC with and without PD-1 inhibition using Nivolumab for the Treatment of newly diagnosed HLA-A2 (02:01)+ H3.3K27M Positive Diffuse Intrinsic Pontine Glioma (DIPG) and newly diagnosed HLA-A2 (02:01)+ H3.3K27M Positive Gliomas**

The following is a list of medications to avoid while you are participating in this study. If you go to any medical visit, please take this list with you for the doctor's reference. Before you begin treatment, Dr. Mueller, or one of her associates will review all medications you are taking. Make sure you talk with your study doctor before you start or stop taking any prescribed or over-the-counter medications. This list contains only a limited sample of common brand names. It is very important to discuss all medications that you are taking with your study doctor. This information will be reviewed at each study visit.

Generic Name	**Brand Name**
Interferon therapy	Intron-A
Allergy desensitization injections	
Corticosteroids (administered by IV or by mouth)	
Growth factors	Procrit Aranesp Neulasta
Interleukins	Proleukin
Illicit drug use	
Any live / attenuated vaccine (e.g. varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose (**Group C only**).	