

PBTC-033 – Summary for Patients and Families

Title: PBTC-033 A Phase I/ II Study of ABT-888, an Oral Poly(ADP-ribose) Polymerase Inhibitor, and Concurrent Radiation Therapy, Followed by ABT-888 and Temozolomide, in Children with Newly Diagnosed Diffuse Pontine Gliomas (DIPG)

This is a brief summary of a clinical trial, a type of therapeutic research study. Clinical trials include only patients who choose, or whose parents permit them to take part in the research study. Participation is entirely voluntary.

Who might be eligible to participate in PBTC-033?

Children who are 21 years old or younger and have a newly diagnosed diffuse intrinsic pontine glioma (DIPG), a type of brainstem tumor, may be eligible. Patients may also be eligible who have had a biopsy of their brainstem tumor, and it has been diagnosed as either anaplastic astrocytoma, glioblastoma multiforme, gliosarcoma or anaplastic mixed glioma. Patients must be able to swallow medications. If patients have had any prior therapy other than surgery and/or steroids, they are not eligible. Patients are also not eligible if their disease has spread beyond the brainstem. Patients will need medical tests to assess whether they can participate in PBTC-033. These tests may include a medical history, physical examination, blood and urine tests and scans (MRI) of the brain and spine (if indicated). Some special imaging techniques, called MRI perfusion/permeability and diffusion tensor imaging (DTI) may be necessary. These additional studies can be done at the same time as your child's standard MRI Brain. About 12-18 children throughout the United States will take part in the Phase I portion of this study. About 60 patients will take part in the Phase II portion.

Why is PBTC-033 being done?

Brain tumors like DIPG, are hard to treat because the usual treatments of radiation and chemotherapy are not very effective. Radiation and chemotherapy cause breaks in DNA (genetic materials inside the tumor cells) and help destroy a tumor. But it is possible that brainstem tumors can fix this DNA damage with a protein in the tumor cells called PARP [Poly(ADP-ribose)] polymerase. Some tumors like DIPG have a high levels of PARP which can undo the effects of radiation and chemotherapy treatment. PBTC-033 tests whether a new drug, ABT-888, that interferes with PARP ("PARP inhibitor") can make brainstem tumors more sensitive to radiation and chemotherapy.

PBTC-033 is a Phase I/II study. The Phase I portion will find the safest dose of ABT-888 that can be given in combination with radiation therapy. The Phase II portion will determine whether the safest dose of ABT-888 combined with radiation therapy, is an effective treatment for children's DIPG.

Patients enrolled in both the Phase I and Phase II portions of PBTC-033 will receive "maintenance therapy" following ABT-888 and radiation therapy. Maintenance therapy is a combination of ABT-888 and Temozolomide (TMZ), another chemotherapy drug. PBTC-033 will also study whether a higher of TMZ (in combination with ABT-888 during maintenance therapy), can be more effective against DIPG than lower doses, which were studied in earlier PBTC clinical trials..

Sometimes a DIPG will look bigger on MRI shortly after radiation (typically within the first 3 to 4 months) but then will get smaller after a few weeks. This finding is called "pseudo-progression" because the tumor did not really "progress" or start to grow again. Researchers believe that pseudo-progression is related to a brain tumor's swelling and inflammation after radiation treatment. Pseudo-progression generally gets better with time.

PBTC-033 includes some special MRI imaging techniques called MRI perfusion/permeability and Diffusion Tensor Imaging (DTI), that hopefully will help tell the difference between true progression in a

tumor versus pseudo-progression. MRI perfusion/permeability and DTI scans take pictures of the brain using the same type of scanner as a regular MRI. **What is involved in this study?**

ABT-888 is an oral medication (liquid or capsule) and must be swallowed twice daily, Monday through Friday for 6-7 weeks during radiation therapy. Your child will then have a rest period for 2-3 weeks.

After the rest period, your child will start maintenance therapy. During maintenance therapy, your child must swallow ABT-888 twice daily. Your child will need to take the morning dose 60-120 minutes before the daily dose of TMZ. Your child will take ABT-888 and TMZ for 5 days a week for a minimum of 28 days “a course of treatment.” Maintenance therapy is scheduled to last for 10 courses. At the end of the 10th course, if your doctor and you agree, your child may continue maintenance therapy for up to an additional 13 courses (23 courses total).

During PBTC-033, your child will have routine medical tests including a physical exam, blood tests, brain scan and a pregnancy test for females of childbearing potential. These tests and procedures are all routine cancer care but may be done more often to monitor your child during PBTC-033. Doctors may also request special tests to help your child or to help them understand how the drug is working.

What are the risks of participating in PBTC-033?

Doctors watch study participants very carefully for any side effects or other problems. However, doctors do not know all the side effect that may occur. Side effects may be mild or very serious. Other medications may be given to lessen side effects. In some cases, side effects may be long lasting or may never go away. This is also a risk of death. Many side effects go away soon after your child stops taking ABT-888 or the combination of ABT-888 and TMZ.

PBTC-033 tests ABT-888 in combination with radiation in children for the first time. Nausea and vomiting are the most commonly reported side effects of when ABT-888 when other chemotherapy drugs are given together. When ABT-888 is given with a chemotherapy drug such as TMZ, the side effects of the chemotherapy drug may get worse. You should talk to your child’s study doctor about any side effects that your child may have while participating in PBTC-033. If you would like more information, please contact the PBTC member institution closest to you. You may also contact the doctor in charge of this study:

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Other information is available through the following:

The National Cancer Institute’s(NCI) Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or through the NCI’s Web site such as www.cancer.gov and www.cancer.gov/clinicaltrials. There is additional accurate and reliable information at www.cancernet.org.