ABSTRACT
This is a multicenter pilot study of SurVaxM (SVN53-67/M57-KLH) for children and young adults with progressive or relapsed medulloblastoma, high grade glioma, ependymoma and newly diagnosed diffuse intrinsic pontine glioma.

Survivin (BIRC5) is an inhibitor of apoptosis (IAP) protein that is highly expressed in many cancers. Survivin's high level of expression in certain pediatric malignancies makes it an attractive molecular target for new therapies, including active specific vaccination-based immunotherapy.

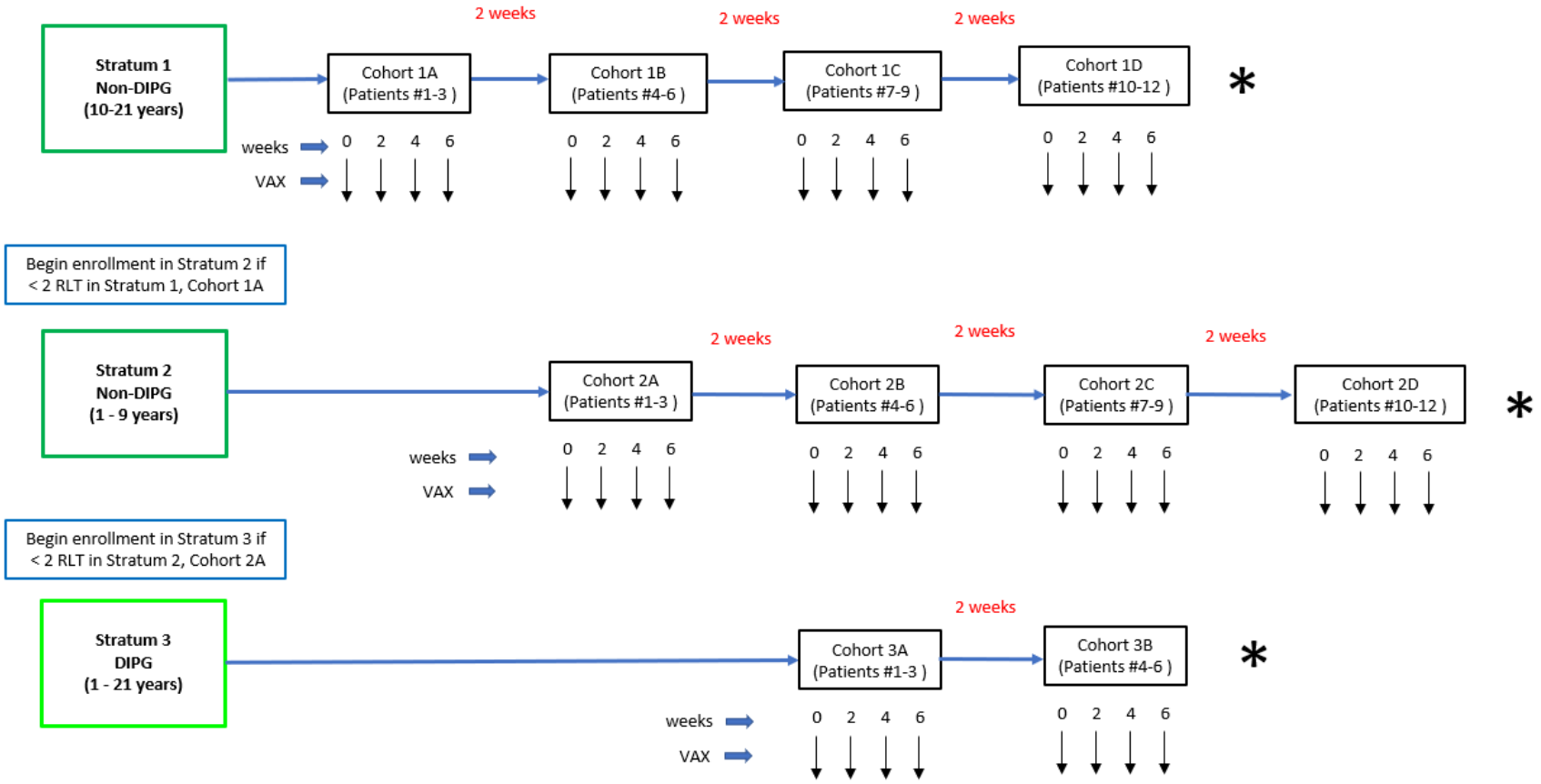
The design of the SurVaxM vaccine employs several strategies to create an effective antitumor immunogen, including: 1) incorporation of multiple MHC class I epitopes, 2) peptide modification to enhance binding to certain MHC class I molecules, 3) cytokine helper support, and 4) antibody-mediated tumor cell killing. All of these effects would not be expected with the unmodified class-I restricted short survivin peptides employed in previously studied glioma vaccines.

There are no prior clinical trials of SurVaxM in pediatric patients; however, SurVaxM has been studied in several adult trials, including a phase I study conducted at Roswell Park Comprehensive Cancer Center. Following the single-institution phase I trial, a multicenter phase IIa trial (NCT024455557) was conducted in 63 patients with newly diagnosed GBM. All patients in this study underwent surgical resection of their tumors. Patients then underwent chemoradiation with temozolomide according to the Stupp protocol. This was followed by a one-month hiatus from chemotherapy, during which priming doses of SurVaxM were initiated. The priming phase of vaccination was then followed by initiation of standard adjuvant chemotherapy with temozolomide and maintenance doses of SurVaxM as an add-on to standard chemotherapy. There have been no regimen-limiting toxicities (RLT) or grade ≥ 3 SAE attributable to SurVaxM, with most toxicities being related to temozolomide. The most common AE was grade 1-2 injection site reaction with 2 patients experiencing Montanide-related granulomatous panniculitis with local skin ulceration at vaccine injection sites, both of which resolved. Humoral and survivin-specific CD8+ T cell responses were observed in almost all patients. Twelve-month overall survival (OS12) was 86% from first immunization and 93.4% from diagnosis. OS12 for meMGMT was 93.1% and unMGMT was 78% from first immunization. Median time to tumor progression (mPFS) was 13.9 months from diagnosis. Although not a randomized trial, these results are superior to overall survival reported in various studies in which patients received standard of care treatment for this disease. A randomized phase IIb clinical trial of standard therapy plus SurVaxM is currently being developed with intent for drug registration, if successful.

The primary objective of this trial is to assess the toxicity profile of SurVaxM in emulsion with Montanide plus sargramostim in children with relapsed or progressive medulloblastoma, high-grade glioma (HGG), or ependymoma and non-recurrent diffuse intrinsic pontine glioma (DIPG) post-radiation therapy (RT). Patients will be enrolled into three separate strata based on age and diagnosis. Enrollment will be staged to allow for safety evaluations between strata (see schema below).

Each patient will receive 500 micrograms SurVaxM as a 1:1 mixture with Montanide ISA 51 in a water-in-oil emulsion. The SurVaxM-Montanide emulsion injection will be followed immediately by sargramostim (or biosimilar) given via a second separate subcutaneous injection in close proximity to the vaccine injection site. Patients will receive four injections administered over a 6-week period, followed by 14 days of follow-up, called the Priming Phase (8 weeks total). Beginning 8-10 weeks after the fourth priming dose, a maintenance dose of SurVaxM with Montanide ISA 51 may be given every 8 weeks ($\pm$ 2 weeks) for two years or until an off-treatment criterion is met.

SCHEMA



* If no progressive disease or RLT, maintenance vaccine may be administered every 8 weeks following initial priming doses

PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given.

Eligibility Criteria for Screening

Tumor

Progressive or Recurrent Patients:
Patients with a histologically confirmed diagnosis of a primary CNS tumor that is progressive or recurrent defined as radiographic progression in any known residual tumor, or the appearance of one or more new lesions, leptomeningeal disease, or new cerebrospinal fluid (CSF) positivity for malignant cells, after most recent treatment modality, see Section 3.2.5. At the time of diagnosis or recurrence, all tumors must have histologic verification of one of the following:

- Medulloblastoma
- Glioblastoma multiforme (GBM)
- Anaplastic astrocytoma
- High-grade astrocytoma, NOS
- Anaplastic oligodendroglioma
- Anaplastic ependymoma (WHO Grade III)
- Ependymoma (WHO Grade II)

Diffuse Intrinsic Pontine Gliomas (DIPG) Patients:
Patients with newly diagnosed diffuse intrinsic pontine gliomas (DIPGs), defined as tumors with a pontine epicenter and diffuse involvement of 2/3 or more of the pons, are eligible without histologic confirmation and will proceed directly to enrollment without screening. See Section 3.2.1)

Tumor tissue

Patients must provide tumor tissue (3 unstained slides or paraffin block) to determine their survivin expression status. Sites should reach out to the PBTC to ensure a slot is available prior to shipping screening specimens, see Section 4.4.3.

Demonstration of survivin expression of at least 1% on tumor tissue by immunohistochemistry is required and must be performed in the central laboratory at Roswell Park Comprehensive Cancer Center (RPCCC) to confirm eligibility. See Section 5.2.1 for additional details.

Age

Patients must be ≥ 1 year of age and ≤ 21 years of age at the time of screening.

Screening Consent

Participant is willing to sign a screening consent. The screening consent is to be obtained according to institutional guidelines. Assent, when appropriate, will be obtained according to institutional guidelines.

Potential Eligibility for Study Enrollment

Patients screened for this trial should be expected to meet the criteria for treatment per Section 3.2.

Eligibility Criteria for Enrollment

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within 21 days prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

Diagnosis

Progressive or Recurrent disease:
Histologic diagnosis (at initial diagnosis or recurrence) of one of the following as defined in Section 3.1.1:

- Medulloblastoma
- Glioblastoma multiforme (GBM)
- Anaplastic astrocytoma
- High-grade astrocytoma, NOS
- Anaplastic oligodendroglioma
- Anaplastic ependymoma (WHO Grade III)
- Ependymoma (WHO Grade II)

Newly diagnosed DIPG:
Patients with diffuse intrinsic pontine gliomas (DIPGs) will be eligible 14 to 56 days post-completion of radiation therapy if they do not have any evidence of progression.

- Patients with a typical DIPG on MR imaging, defined as a tumor with a pontine epicenter and diffuse involvement of more than 2/3 of the pons, are eligible without histologic confirmation.
    - Note: Patients with typical DIPG who undergo a biopsy are eligible provided the tumor is a diffuse glioma WHO Grade II-IV with OR without H3 K27M mutation.
- Patients with pontine lesions that do not meet these MR imaging criteria will be eligible if there is histologic confirmation of diffuse glioma WHO Grade II-IV with H3 K27M mutation.

Please see Section 4.4.2 for details regarding Special Instructions for Patient Enrollment.

Demonstration of survivin expression

For patients with relapsed or progressive medulloblastoma, HGG, or ependymoma, demonstration of survivin expression as assessed after screening consent/assent of at least 1% on tumor tissue by immunohistochemistry (IHC) is required and must have been performed in the central laboratory at Roswell Park Comprehensive Cancer Center (RPCCC) to confirm eligibility.

For patients with DIPG, diagnostic biopsy for histologic confirmation is not required, and tumor expression of survivin is therefore not required for eligibility for these patients.

Disease Status

Patients must have evaluable disease within the central nervous system to be eligible. Evaluable disease includes either measurable OR non-measurable disease, defined as follows:

- Measurable disease: bi-dimensionally measurable disease; at least one lesion that can be accurately measured in at least two dimensions (per guidelines in Section 12.1.2).
- Non-measurable disease:
    - A lesion that does not meet the criteria for measurable disease as defined above; or
    - diffuse leptomeningeal disease, or
    - no tumor visible on imaging but presence of malignant cells on cytologic examination of CSF.

Age

- Stratum 1 (progressive or recurrent) patients must be ≥10 years of age and ≤ 21 years of age at the time of study screening.
- Stratum 2 (progressive or recurrent) patients must be ≥1 year of age and < 10 years of age at the time of study screening.
- Stratum 3 (newly diagnosed DIPG) patients must be ≥1 year of age and ≤ 21 years of age at the time of study enrollment

Prior Therapy

- Patients with recurrent or progressive disease must have received prior chemotherapy and/or radiotherapy.
- Patients with newly diagnosed DIPG must have completed radiation therapy (see Section 3.2.5.3).
- Patients must have recovered from the acute treatment related toxicities (defined as ≤ Grade 1 if not defined in eligibility criteria; excludes alopecia) prior to entering this study.

Chemotherapy

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if nitrosourea. Patients must have received their last dose of non-myelosuppressive chemotherapy at least 7 days prior to enrollment.

Investigational/Biologic Agent

- Biologic or investigational agent (anti-neoplastic):

Patient must have received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.

    - For agents that have known adverse events occurring beyond 7 days after

administration, this period must be extended beyond the time during which adverse events are known to occur.

- Monoclonal antibody treatment and agents with known prolonged half-lives:

Patient must have received their last dose of the agent ≥ 28 days prior to study enrollment.

Radiation

Patients with recurrent or progressive CNS tumor must have had their last fraction of:

- Craniospinal irradiation, whole brain radiation, total body irradiation or radiation to spine ≥ 6 weeks (42 days) prior to enrollment.
- Focal irradiation ≥ 14 days prior to enrollment.

DIPG Patients:

- Patients with DIPG are eligible after completion of initial radiotherapy (with or without concurrent treatment) and in the absence of progressive disease on post-radiation imaging. Patients must have completed radiation therapy at least 14 days prior to enrollment but no longer than 56 days and cannot have received any other tumor-directed treatment except the following:
    - Patient may have received temozolomide or other non-investigational agents during irradiation at the treating physician's discretion. If the patient has received such agents concurrently with radiation, then patient must have recovered from the acute treatment related toxicities (defined as < Grade 1) prior to enrollment.

Cellular Therapy

Patient must be:

- ≥ 24 weeks (168 days) since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease.
- ≥ 12 weeks (84 days) since autologous stem cell transplant prior to enrollment.
- > 42 days since completion of any other type of adoptive cellular therapy prior to enrollment.

Cranial Surgery

Patients must be at least 14 days from recent cranial surgery (VP shunt, ETV, tumor resection) at the time of enrollment.

Neurologic Status

Patients with neurological deficits should have deficits that are stable for a minimum of 7 days prior to enrollment. A baseline neurological exam should clearly document the neurological status of the patient at the time of enrollment on the study.

Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 14 days prior to enrollment must be ≥ 60. Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered

ambulatory for the purpose of assessing the performance score.

Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 0.75 x 10^9 cells/L
- Platelets ≥ 100 x 10^9 cells/L (unsupported, defined as no platelet transfusion within 7 days prior to enrollment)
- Hemoglobin ≥ 8 g/dL (may receive transfusions)
- PT,INR, PTT or aPTT ≤ 1.5 x ULN
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- ALT(SGPT) and SGOT (AST) ≤ 3 x institutional upper limit of normal (ULN)
- Albumin ≥ 2 g/dL
- Blood creatinine based on age/gender as noted in Table 3.6.7. Patients that do not meet the criteria in Table 3.6.7 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible.

Table 3.6.7 Blood Creatinine for age/gender

Age	**Maximum Blood Creatinine (mg/dL)**	
	Male	**Female**
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

Infectious Diseases

- *Human Immunodeficiency Virus (HIV) Infected Individuals*

Patients who are known to be Human immunodeficiency virus (HIV)-infected must be on effective anti-retroviral therapy with undetectable viral load for 24 weeks (168 days) prior to study enrollment.

- *Hepatitis B Chronically Infected Individuals*

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

- *Hepatitis C (HCV) Infected Individuals*

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

Corticosteroids

Patients who are receiving dexamethasone must be on a stable or decreasing dose for at least 7 days prior to enrollment. A maximum dose of 0.1 mg/kg/day (and maximum total daily dose 4 mg) of dexamethasone (or equivalent) is permitted at study entry. Effort should be made to reduce to lowest tolerated steroid dose.

Patients must be willing to use brief courses (at least 72 hours) of steroids as directed for potential inflammatory side effects of the therapy if recommended by their treating physician.

Growth Factors

Patients must be off all colony-forming growth factor(s) for at least 14 days prior to enrollment (e.g., filgrastim, sargramostim, or erythropoietin). Fourteen (14) days must have elapsed if the patient received a long-acting formulation.

Pregnancy

Pregnant women or nursing mothers are excluded from this study because SurVaxM is an agent with the potential for teratogenic effects. Female patients of childbearing potential must have a negative serum or urine pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnancy Prevention

Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.

Informed Consent

The patient or parent/guardian can understand the consent and is willing to sign a written informed consent document according to institutional guidelines. Assent, when appropriate, will be obtained according to institutional guidelines.

Exclusion Criteria

Breast-feeding Women

Female patients who are breastfeeding are not eligible for this study unless they agree not to breastfeed because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with SurVaxM.

Excluded Diagnoses

- Patients with spinal cord primary tumors
- Patients with relapsed or progressive DIPG

- Patients with metastatic DIPG are not eligible. MRI of spine must be performed if disseminated disease is suspected by the treating physician.
- Patients with midline high grade gliomas including those with H3 K27M-altered diffuse midline glioma (DMG) centered outside of the pons
- Patients with Grade II myxopapillary ependymoma
- Patients with WHO Grade I or II gliomas are not eligible unless tumor is defined as a DIPG (see Section 3.2.1).
- Patients with bone-only metastatic lesions that do not have otherwise evaluable CNS disease.

Bulky Disease

Patients with bulky tumor on imaging are ineligible. Bulky tumor is defined as any of the following:

- Tumor with evidence of clinically significant tonsillar herniation
- Tumor with evidence of clinically significant uncal herniation causing midbrain compression or midline shift greater than 5 mm
- Tumor with a diameter >4cm in one dimension on T2/FLAIR
- Tumor that in the opinion of the site investigator, shows significantly rapid progression of mass effect in either the brain or spinal cord such that the priming phase of vaccination (i.e., 6 weeks) cannot be completed before clinical deterioration is likely to occur.

Treating physicians should contact the Study Chair to request a rapid central imaging review to confirm fulfilment of these eligibility criteria, if they have concerns. If clinically appropriate, surgical debulking of large tumors should be considered before study entry.

Concurrent Illness

- Active, uncontrolled infection requiring treatment (including HIV infection)
- Patients with active autoimmune disease or documented history of autoimmune disease/syndrome that requires ongoing systemic steroids or systemic immunosuppressive agents, with the exception of:
    - Patients with vitiligo or resolved asthma/atopy
    - Patients with hypothyroidism stable on hormone replacement or Sjogren's syndrome
- History of or ongoing pneumonitis or significant interstitial lung disease
- Patients with any clinically significant unrelated systemic illness (significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial.
- Any medical condition that, in the opinion of the Principal Investigator, would compromise the patient's ability to participate in the study.

Concomitant Medications

- Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.
- Patients who are receiving any cannabidiol (CBD) or medical marijuana treatment are ineligible.
- Patients who have received the last vaccination of a live vaccine ≤ 30 days prior to enrollment are ineligible.
    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and must meet timeline for live vaccine.
- Patients who have received an inactivated virus, peptide, or mRNA vaccine within 14 days of the start of protocol therapy are ineligible.
- Patients may not be on immunosuppressive therapy, including corticosteroids (except as defined in Section 3.2.10) at time of enrollment. However, patients who require intermittent use of bronchodilators, local steroid injections, or topical steroids will not be excluded from the study.
- Patients may not be receiving allergy desensitization injections or interleukins at the time of enrollment.

Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity of therapy or to adhere to drug administration plan, other study procedures, and study restrictions.

Allergy

Known allergy or hypersensitivity to Keyhole Limpet Hemocyanin (KLH), granulocyte colony-macrophage stimulating factor (sargramostim) or MRI contrast agent.

Bleeding Disorder

Patients with a known coagulopathy or bleeding diathesis or requires the use of systemic, anticoagulant medication are not eligible.

Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC

Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

The PBTC remains committed to offering participation in our trials to subjects of all races and ethnic groups.

Treatment at the Primary Institution

All experimental protocol therapy should be administered and all on treatment imaging studies should be obtained at a PBTC institution. Laboratory studies, excluding pharmacokinetic and biologic assays, may be performed at a CLIA certified laboratory of the investigator's choice. Imaging utilized to determine eligibility may be performed at an outside institution if all required imaging sequences are included and the study is deemed of adequate quality by the treating team. All required physical examinations, laboratory parameters need to be performed at the primary PBTC institution during the Priming Phase of the protocol.

Criteria to Start Treatment

- Subjects must start therapy within 7 days of enrollment.
- Laboratory values must be no older than 7 days prior to the start of therapy. If a test that is repeated post enrollment and prior to the start of therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If rechecks are still outside the limits for eligibility, the patient may not receive protocol therapy and will be considered off study.