

Study Title: Intra-Arterial (IA) Chemotherapy for Newly Diagnosed, Residual, or Recurrent Atypical Choroid Plexus Papilloma (ACPP) and Choroid Plexus Carcinoma (CPC) Prior to Second-Look Surgery

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Statement of Compliance

(1) [The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

AE	Adverse Event
ACPP	Atypical Choroid Plexus Papilloma
CBL	Calculated Blood Loss
COG	Children's Oncology Group
CPC	Choroid Plexus Carcinoma
CPP	Choroid Plexus Papilloma
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
EOR	Extent of Resection
ERG	Avian v-ets Erythroblastosis Virus E26 Oncogene Homolog
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GTR	Gross Total Resection
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IA	Intra-arterial
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
Rb	Retinoblastoma
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine
WHO	World Health Organization

1. Protocol Summary

Full Title: Intra-Arterial (IA) Chemotherapy for Newly Diagnosed, Residual, or Recurrent Atypical Choroid Plexus Papilloma (ACPP) and Choroid Plexus Carcinoma (CPC) Prior to Second-Look Surgery.

Short Title: IA chemotherapy for ACPP and CPC

Clinical Phase: Phase 1

Principal Investigator: Mark M. Souweidane, MD

Study Description:

Complete surgical resection of ACPP or CPC is the single most important prognostic variable for long-term survival. However, accomplishing a complete surgical resection is frequently hampered by the voluminous size and vascularity of these tumors in young children with a proportionally small circulating blood volume. Pre-operative systemic chemotherapy is known to reduce tumor volume and intra-operative blood loss thereby facilitating an optimal total 2nd look surgical removal of ACPPs and CPCs, but this approach is limited by systemic toxicity and dose-limiting side effects.

We propose using intra-arterial (IA) chemotherapy, a procedure that has not been assessed in ACPP or CPC, as a pre-operative strategy prior to 2nd look surgery. IA chemotherapy reduces systemic exposure and associated toxicity, while providing higher drug concentrations in a vascular defined domain. Pre-operative IA chemotherapy is accepted as a beneficial strategy in many solid tumors as it has shown to simplify 2nd look surgery. IA chemotherapy is now standard of care in ocular retinoblastoma (Rb).

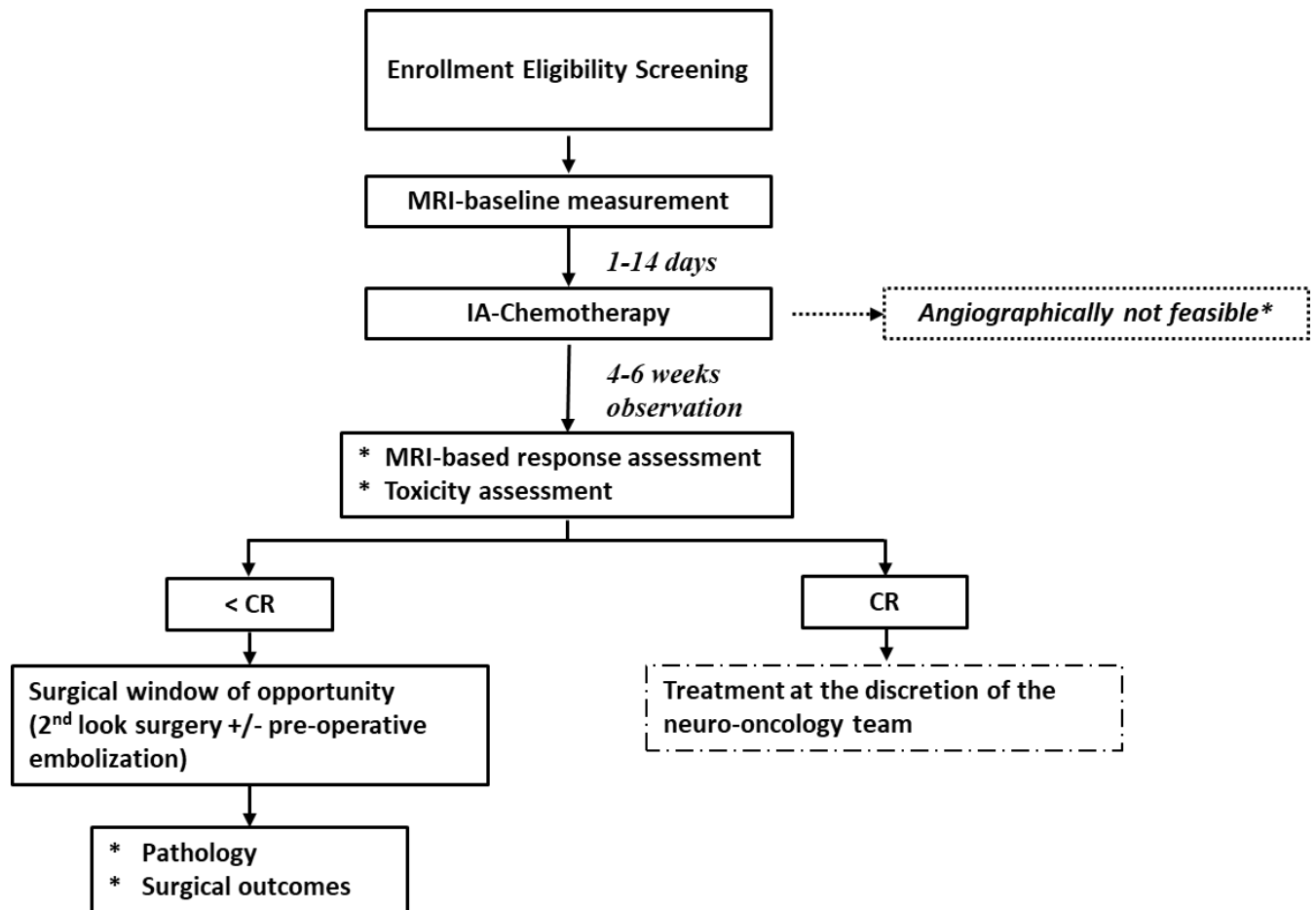
The intent of this protocol is to adopt the pre-existing IA chemotherapy strategy and establish it as a safe pre-operative bridge to potentiate the goals of 2nd look surgery for ACPP and CPC. We hypothesize that pre-operative super-selective IA chemotherapy for newly diagnosed, residual, or recurrent ACPP/CPC in children/adults is safe. We further hypothesize that IA chemotherapy for ACPP and CPC is feasible and will result in decreased tumor volume and vascularity (i.e. perfusion). This strategy may ultimately potentiate the goals of 2nd look surgery.

Sample Size: N=6 for the treatment plan

Enrollment: This study will enroll 6 subjects for the treatment plan and screen up to 12 subjects.

Study Population:	Subject of any age with newly diagnosed, residual, or recurrent ACPP/CPC. We anticipate majority of subjects to be children but will also enroll eligible adults.
Enrollment Period:	2 years
Study Design:	This is a single-arm, single site, open-label, Phase 1, pilot study with an intervention of pre-operative intra-arterial chemotherapy for newly diagnosed, residual or recurrent ACPP/CPC in children prior to 2 nd look surgery.
Description of Sites/ Facilities Enrolling Participants:	Weill Cornell Medicine Pediatric Brain and Spine Center
Study Duration:	2020-2024
Participant Duration:	11 weeks + 1 year follow-up
Study Agent/Device Name	IA chemotherapy
Intervention Description:	Pre-operative IA chemotherapy
Primary Objectives:	<ol style="list-style-type: none"> 1. To establish the safety of a single dose of IA chemotherapy in subjects with newly diagnosed, residual, or recurrent ACPP/CPC.
Secondary Objectives:	<ol style="list-style-type: none"> 1. To assess the feasibility of delivering a singular treatment of IA chemotherapy in subjects with newly diagnosed, residual, or recurrent ACPP/CPC. 2. To assess radiographic response of a single dose of IA chemotherapy in subjects with newly diagnosed, residual or recurrent ACPP/CPC. 3. Using 2nd look surgery as a window of opportunity to assess surgical outcomes (extent of resection (EOR), calculated blood loss (CBL), % blood loss, transfusion needs, etc.) following a single dose of IA chemotherapy with or without embolization. 4. Using 2nd look surgery as a window of opportunity to assess pathology correlates (tumor vascularity, tumor viability, etc.) following a single dose of IA chemotherapy with or without embolization.
Primary Endpoint:	<ol style="list-style-type: none"> 1. Serious adverse events (SAEs) related to IA chemotherapy
Secondary Endpoints:	<ol style="list-style-type: none"> 1. Rate of angiographic procedural success (screen failures, technical failures, etc.) 2. Degree of tumor volume and tumor perfusion reduction using MRI 3. Measurements of EOR, CBL, and % blood loss 4. Pathology correlates of vascularity and tumor viability

1.1 Study Schema



*: In the event that the angiography procedure is not suitable for a subject, the subject will not be eligible to participate in the treatment plan. Therefore, this subject will not be counted as one of the six total subjects in the treatment plan. However, this subject will be part of the endpoint analysis to measure the rate of angiographic procedural success. “Angiographically not feasible” would include screen failures, technical failures, etc.

1.2 Study Objectives

1.2.1 Primary Objectives:

1. To establish the safety of a single dose of IA chemotherapy in subjects with newly diagnosed, residual, or recurrent ACP/CPC.

1.2.2 Secondary Objectives:

1. To assess the feasibility of delivering a singular treatment of IA chemotherapy in subjects with newly diagnosed, residual, or recurrent ACP/CPC.
2. To assess radiographic response of a single dose of IA chemotherapy in subjects with newly diagnosed, residual or recurrent ACP/CPC.
3. Using 2nd look surgery as a window of opportunity to assess surgical outcomes (extent of resection (EOR), calculated blood loss (CBL), % blood loss, transfusion needs, etc.) following a single dose of IA chemotherapy with or without embolization.
4. Using 2nd look surgery as a window of opportunity to assess pathology correlates (tumor vascularity, tumor viability, etc.) following a single dose of IA chemotherapy with or without embolization.

2. Background

2.1 Choroid plexus tumors

Choroid plexus tumors are rare malignant central nervous system tumors accounting for 3 % of all brain tumors in children (Ostrom et al., 2016). According to the 2016 World Health Organization (WHO) classification, choroid plexus tumors are classified based on histological criteria as choroid plexus papilloma (CPP) or grade I tumor, atypical choroid plexus papilloma (ACPP) or grade II tumor, and choroid plexus carcinoma (CPC) or grade III tumor. CPCs differ from CPPs in that they most frequently arise within the lateral ventricle, are frequently invasive, and have a poor prognosis (Gopal, Parker, Debski, & Parker, 2008; Sun et al., 2014). In this proposal, we plan to enroll subjects with newly diagnosed, residual or recurrent ACP/CPC. We anticipate majority of the subjects to be children between ages 0-21. However, ACP/CPC can occasionally occur in adults and we will also enroll subjects from that population if they are eligible.

Three types of choroid plexus tumors:

CPP:

CPPs tend to mimic papillary choroid plexus morphology in its radiologic, “cauliflower appearance” but have an increased number of cells, sometimes stratified and with elongated shape. They can present with areas of calcification and cystic or haemorrhagic regions but, by definition, do not invade the brain parenchyma. Oncocytic alterations, xanthogranulomatous reaction, and/or melanin pigment deposition can be identified. By definition, they are benign and curable with surgical gross total resection.

Atypical CPPs (ACPP):

ACPPs are composed of cells showing any sign of atypical but confined to the ependymal lining of the ventricles. Their most distinctive feature is increased mitotic activity defined as two or more

mitoses per ten randomly selected high-power fields. ACPs have an increased risk of recurrence when compared to CPP.

CPC:

In contrast, CPCs show mitotic figures (five or more mitoses per ten randomly selected high-power fields), nuclear atypia, increased nuclear-to-cytoplasmic ratio, and necrosis. The papillary architecture is distorted and there is diffuse invasion of the adjacent neural tissue by the infiltrating cells on a stromal base. CPCs are malignant due to their potential for recurrence and dissemination.

Clinical features:

Choroid plexus tumors are found within the ventricles arising from the choroid plexus. Their location is somewhat dependent on pathologic grade and age with younger patients having a preponderance in the lateral ventricles, 40% in the fourth ventricle, 5% in third ventricle, and 5% in multiple ventricles.

Radiographic studies typically demonstrate a large, hyperdense, contrast-enhancing, intraventricular mass. Approximately 90% of CPC patients present with signs of hydrocephalus. In infants, increased intracranial pressure often manifests as enlarged head circumferences, development delay, bulging fontanelles, splayed sutures, strabismus, and vomiting.

Pathologic features:

The pathology of CPCs typically shows a friable papillary or “cauliflower-like” appearance. Intraoperatively, CPCs may be loosely or densely adherent to the ventricular wall and typically invade the adjacent brain parenchyma. On sectioning, the tumors display solid areas intermixed with necrotic and hemorrhagic foci. Other microscopic features include frequent mitoses, nuclear pleomorphism, and sheet-like growth. The Ki67 (MIB-1) labeling index is typically elevated with a reported range of approximately 4-30%. About 50% of CPC are characterized molecularly by TP53 mutations (Tabori et al., 2010).

Prognostic factors:

ACPs and CPCs usually grow rapidly and have a 5-year survival rate of approximately 89% and 40%, respectively (Wrede et al., 2009). Treatment of ACP and CPC is challenging. Gross total resection allows for the best chance of survival and improves the overall prognosis. However, surgery is difficult because efforts at total resection are hindered by the tumor’s invasive tendencies. Some data indicated that that almost half of patients with CPCs that have sub-total resections showed significantly worse 5 year survival rates (Fitzpatrick, Aronson, & Cohen, 2002). Radiation as adjuvant therapy is currently not being used in young children due to severe negative neurodevelopmental effects and the risk of secondary malignancies (Sun et al., 2014). Neoadjuvant systemic chemotherapy to reduce tumor vascularity prior to surgery has been considered as the optimal approach to achieve 2nd look surgical resection of the tumor. However, administering systemic chemotherapy to young children, either as a neoadjuvant or an adjuvant approach, is accompanied

by numerous toxicity effects and serious, disabling or life-threatening health conditions later in life (Abramson, Francis, & Gobin, 2019; Hudson et al., 2013; Lafay-Cousin et al., 2010).

2.2 Investigational Agent/Device, or Surgical Treatment/Method

Cerebral Angiography: The basic concept of cerebral angiography involves the navigation of a catheter up through the vasculature to the aortic arch then the major vessels that supply the cerebral circulation. These vessels include the carotid arteries and the vertebral arteries. Angiography begins with arterial access. This usually involves the puncture and cannulation of the right or left femoral artery using the Seldinger technique. Local anesthetic is applied to the femoral skin and a single wall puncture needle is used to access the artery. Once the artery is entered then a wire is passed through the puncture needle into the artery and the needle is exchanged for an introducer sheath. The original wire is then removed. The introducer sheath is connected to a continuous heparinized saline flush. This introducer sheath then becomes the portal of entry for the diagnostic catheter. Under direct visualization of fluoroscopy, the diagnostic angiography catheter is then passed through the introducer sheath up the femoral artery, iliac artery and into the descending aorta with the use of a guide wire. This guide wire is later used to access the cerebral vasculature. The catheter wire combination is used to cannulate the internal carotid and vertebral arteries bilaterally. There, a cerebral angiogram is performed over the cranium in antero-posterior and lateral views. The arteries leading to the ACP or CPC are identified: anterior choroidal artery, median or lateral posterior choroidal arteries, and potentially others depending on tumor location.

Super-selective angiography and IA chemotherapy procedure: The patient is given a heparin bolus to obtain an automated coagulation time of two to three times baseline (usually 50-80 units/kg). The catheter is placed in the cervical segment of the internal carotid or vertebral artery. A new roadmap image is generated and now the micro catheter is introduced with a micro-guide wire. One of the specific arteries leading to the tumor is identified and the micro-guide wire is advanced into this vessel. The micro-catheter is then subsequently advanced over this micro-guide wire and the guide wire is removed. A super-selective angiogram is then performed by injecting contrast through the micro catheter to confirm that it is in the desired vessel, in this case the vessel supplying the territory containing the brain tumor. Even more super selective catheterization can be performed in order to localize the lesion more specifically. Once the desired catheter position has been achieved the infusion of melphalan, topotecan and/or carboplatin will be performed over the specified time course. Then, the other arteries supplying the tumors are similarly catheterized and infusion of chemotherapy is performed. On the completion of the infusion the micro catheter is removed, and an angiogram is performed to check the cerebral circulation before the catheter and introducer sheath are removed. Homeostasis is achieved at the femoral artery with manual compression.

IA Chemotherapeutic Agents for ACP or CPC: Chemotherapy drug combinations consist of melphalan, topotecan and/or carboplatin will be used in this protocol. Rationale for drug choice and drug combinations are described in sections 2.3 and 7.

Pre-operative IA Embolization: At the discretion of the neurosurgical team, 2nd look surgery will be performed with or without pre-operative embolization. Rationale for this strategy is described in section 2.3.

2.3 Rationale:

ACPP or CPC is a devastating malignant brain tumor that mainly occurs in children. Due to its rarity, treatment remains controversial and challenging. Among the different treatment modalities, complete surgical removal is the single most important prognostic variable for long-term survival (Gopal et al., 2008; Sun et al., 2014; Wrede et al., 2009). However, accomplishing a complete surgical resection is frequently hampered by the voluminous size and vascularity of these tumors in young children with a proportionally small circulating blood volume. Pre-operative systemic chemotherapy is known to reduce tumor volume and intra-operative blood loss thereby facilitating an optimal total 2nd look surgical removal of ACPPs and CPCs (Lafay-Cousin et al., 2010; Passariello et al., 2015; Schneider et al., 2015; Souweidane, Johnson, & Lis, 1999). This approach, however, is limited by systemic toxicity and dose-limiting side effects. Therefore, alternative pre-operative strategies are needed to accomplish a maximum reduction in tumor volume and vascularity in order to potentiate successful complete 2nd look surgical resection, while minimizing toxicity and dose limitation associated with systemic chemotherapy.

We propose using IA chemotherapy, a procedure that has not been assessed in atypical CPP or CPC, as a pre-operative strategy prior to 2nd look surgery. IA chemotherapy is a minimally invasive procedure that delivers chemotherapy agents directly to the site of the tumor via the intra-arterial route. IA chemotherapy reduces systemic exposure and associated toxicity, while providing higher drug concentrations in a vascular defined domain. Pre-operative IA chemotherapy is accepted as a beneficial strategy in many solid tumors as it has shown to simplify 2nd look surgery (Kemeny et al., 2009; Lian et al., 2019; Liu et al., 2018). The technical capability of this strategy in infants is established and is now standard of care in ocular retinoblastoma (Rb)(Abramson, Dunkel, Brodie, Kim, & Gobin, 2008; Abramson, Dunkel, Brodie, Marr, & Gobin, 2010; Gobin, Dunkel, Marr, Brodie, & Abramson, 2011). Such a treatment modality is perfectly suited for ACPP and CPC which parallels Rb in its angio-architectural principle and has a clinical need for an alternative pre-operative strategy.

IA chemotherapy is an appealing pre-operative strategy for ACPP and CPC prior to 2nd look surgery. First, IA chemotherapy of ACPP and CPC allows for enriched drug concentration at the site of the tumor while avoiding off target effects. This is highly achievable because CP tumors not only recapitulates some of the features of Rb, it also has its own distinctive and favorable anatomy as it relates to IA chemotherapy. While the ophthalmic artery that carries the blood supply to Rb is connected to the entire ocular domain where it resides, the dominant artery for CP tumors is exclusive to the tumor domain. Second, IA chemotherapy for ACPP and CPC has the potential for greater reduction in tumor volume and vascularity compared with systemic chemotherapy, a strategy that greatly potentiates the goals of 2nd look surgery. For example, IA chemotherapy has been shown to reduce microvasculature of colorectal carcinomas and in Rb, it has resulted in more advanced eyes

salvaged when compared with chemotherapy or radiation (Chantada & Schaiquevich, 2016; Lin et al., 2002).

IA chemotherapy for ACPP and CPC prior to 2nd look surgery could revolutionize the treatment of this malignancy, resulting in improved prognosis and outcomes. The intent of this protocol is to adopt the pre-existing IA chemotherapy strategy and establish it as a safe pre-operative bridge to potentiate the goals of 2nd look surgery for ACPP and CPC. We hypothesize that pre-operative super-selective IA chemotherapy for newly diagnosed, residual, or recurrent ACPP and CPC in children/adults is safe. We further hypothesize that IA chemotherapy for ACPP and CPC is feasible and will result in decreased tumor volume and vascularity (i.e. perfusion). This strategy may ultimately potentiate the goals of 2nd look surgery.

2.3.1 Rationale for pre-operative IA chemotherapy

- ***IA chemotherapy as a well-established pre-operative strategy in a variety of solid tumors***

IA chemotherapy is a well-established pre-operative strategy commonly used for a variety of tumors. For several tumor types including liver tumor, soft tissue sarcoma, pancreatic cancer and bladder cancer, preoperative IA has been shown to simplify surgical removal and improve outcome (Lian et al., 2019; Liu et al., 2018). The IA chemotherapy approach for liver tumors called hepatic arterial infusion (HAI) chemotherapy maximizes hepatic drug exposure by delivering the drug via hepatic artery. Multiple clinical trials have confirmed HAI resulted in higher response rate than those seen with systemic chemotherapy and ultimately improved gross total resection (GTR) rate (Kemeny et al., 2009).

- ***IA chemotherapy is the mainstay treatment option for children with Rb***

Classic treatment options for children diagnosed with Rb include enucleation, external-beam radiotherapy, systemic chemotherapy, and focal therapies, such as cryotherapy, thermotherapy, laser photocoagulation, and plaque radiotherapy (Jabbour et al., 2012). However, each treatment modality has limitations and risk factors (Wyse et al., 2016). Enucleation, although life-saving and straightforward, leads to permanent loss of vision and can be devastating for patients harboring bilateral tumors. External beam radiotherapy has deleterious local and systemic consequences, including cataract formation, ocular dryness, facial dysmorphism, and secondary cancers. Systemic chemotherapy can effectively treat Rb and provide impressive long-term control, however, has limited efficacy for advanced Rbs and is toxic to the developing body of young children.

The modern IA chemotherapy emerged in the past decade and has become a mainstay treatment option for Rb. It is a minimally invasive approach that delivers chemotherapy agents by the intra-arterial route. In the case of Rb, chemotherapy agents are delivered selectively into the ophthalmic artery and provides drastic improvements over the classic treatments. First, it minimizes systemic absorption and drug related toxicity such as neutropenia, infection, the need for transfusion, and secondary neoplasm. Second, it allows for highly effective drugs such as melphalan, which is too toxic

for systemic administration, to be used. Lastly, higher doses of chemotherapy agents can be delivered directly to the tumor, which increase the biological effect, enhance tumor control and reduce the rate of recurrence (Shields & Shields, 2010).

Multiple clinical trials over the past decade have demonstrated an impressively high rate of eyes salvaged as a result of IA chemotherapy for the treatment for Rb of various grades (Tables 1 and 2). (Abramson et al., 2008; Abramson et al., 2010; Abramson et al., 2012; Bracco et al., 2013; Choi et al., 2013; Gobin et al., 2011; Palioura et al., 2012; Peterson, Elhammady, Quintero-Wolfe, Murray, & Aziz-Sultan, 2011; Shields et al., 2011; Shields et al., 2012; Shields et al., 2014; Thampi et al., 2013; Vajzovic et al., 2011; Venturi et al., 2013).

Table 1:

Reese-Ellsworth classification of Rb	
Low grade tumors (I-III) eyes	57
High grade tumors (IV-V) eyes	137
Prior treatment	74
Eyes salvaged	152 (78%)
Eyes enucleated	42 (22%)

Table 2:

International Classification of Rb	
Low grade tumors (A-C) eyes	66
High grade tumors (D-E) eyes	221
Prior treatment	167
Eyes salvaged	233 (71%)
Eyes enucleated	94 (29%)

Tables 1 and 2: IA chemotherapy for Rb from 16 studies published since 2008. Patients were grouped by either the Reese-Ellsworth or International classification system for Rb. IA chemotherapy alone or in conjunction with other treatments were used. Eyes salvaged and enucleated were used as end-point measures (modified from (Wyse, Handa, Friedman, & Pearl, 2016)).

- ***Toxicity and limitations associated with systemic chemotherapy***

Systemic chemotherapy either as a neoadjuvant or an adjuvant approach for both young children and adults has major disadvantages (Gobin et al., 2011; Wyse et al., 2016). Systemic chemotherapy is an ongoing treatment that lasts for weeks to months. The common side effects include hair loss, nausea, vomiting, constipation, diarrhea, mouth sores, increased risk of infection, increased bleeding and bruising, and fatigue. Less common complications include kidney damage, nerve damage and increased risk for second malignancies. In addition, there are long-term health problems associated with systemic chemotherapy for childhood cancer. A study of 1700 adults ages 18-60 who survived cancer as children, showed treatment with chemotherapy, radiation or both is associated with high prevalence of diseases in a range of organs from the brain, the heart, the endocrine system to the lung (Hudson et al., 2013).

2.3.2 Rationale for 2nd look surgery after IA chemotherapy

- ***Surgical complications of CPC without pre-operative chemotherapy***

Gross total resection of CPC allows for the best chance of survival and improves prognosis. Several meta-analyses have shown that 5-year survival rate is 58.1% in gross total resection compared with

20.9% in subtotal resection (Sun et al., 2014). However, surgical resection of CPC is dangerous and has a high rate of surgical related mortality and morbidity given the young patient population, large volume and marked vascularity of the tumor. In general, complete resection has only been achieved in 40-50% of the children with CPC (Fitzpatrick et al., 2002; Packer et al., 1992; Pierga, Kalifa, Terrier-Lacombe, Habrand, & Lemerle, 1993). In one contemporary study, surgical related mortality due to excessive hemorrhagic complications remains as high as 30% (Pencalet et al., 1998).

- ***Greater success of 2nd look surgery of ACPP and CPC after pre-operative systemic chemotherapy***

Systemic chemotherapy followed by a definitive surgery offers optimal resection of ACPPs and CPCs (Greenberg, 1999; Lafay-Cousin et al., 2010; Passariello et al., 2015; Schneider et al., 2015; Souweidane et al., 1999; St Clair et al., 1991). Two mechanisms are involved when chemotherapy is given preoperatively, resulting in a greater success of surgical resection. One mechanism is through the obvious tumoricidal or cellular effect resulting in a reduction of tumor volume, thereby increasing the prospect of aggressive surgical removal. We and Passariello et al. have documented volumetric tumor reduction using preoperative chemotherapy in ACPP and CPC with subsequent total removal (Passariello et al., 2015; Souweidane et al., 1999). Another mechanism is the vascular reduction of these tumors thus having obvious beneficial impact on the potential for safe and meaningful surgical removal. The support for this mechanism has been demonstrated by at least two studies from the Hospital for Sick Children in Toronto in recent years. Blood loss due to resection was reduced from 96% in children without therapy compared to 22% in children with neoadjuvant chemotherapy. As a result, these studies reported a high rate of complete or near-complete 2nd look resection (Lafay-Cousin et al., 2010; Schneider et al., 2015).

2.3.3 Rationale for the possibility of embolization prior to 2nd look surgery

At the discretion of the neurosurgical team, embolization strategy would be considered prior to 2nd look surgery. Intra-arterial embolization is an adjunctive therapy normally done to devascularize the tumor prior to surgical resection. Over the past 3 decades, it has been done as a pre-operative procedure in various types of tumor. It is especially a beneficial procedure to tumors of the spine, head and neck that have relatively large blood vessels supplying the tumors (Lazzaro et al., 2011; Zahringer et al., 2005). In recent years, pre-operative embolization has been done in children diagnosed with CPC. Pre-operative embolization followed by second-look surgery of CPCs reduced the amount of intra-operative blood loss, resulted in higher rates of total resection and lower operative morbidity and mortality (Haliasos et al., 2013; Slater, Hoffman, Drake, & Krings, 2016; Wang et al., 2013).

2.3.4 Rationale for the design of response criteria (detailed in section 10)

The primary aim of the protocol is to establish the safety of one dose of IA chemotherapy on ACPP or CPC. The secondary aims are designed to establish the feasibility and to assess the radiographic, surgical, and pathologic effects of one dose of IA chemotherapy. The radiographic assessment will measure the effect of a single therapeutic intervention. The surgical features and pathologic interpretation, however, cannot be solely attributed to the investigational intervention of IA chemotherapy. Since children may be treated with preoperative embolization it would be impossible

to separate out effects due to IA chemotherapy from embolization. We anticipate using published historical data on surgical parameters (defined in section 10.2) and pathologic features (defined in section 10.3) as benchmarks for our results. Claims related to the beneficial effects of IA chemotherapy on surgical and pathologic features will likely not be possible but these outcome measures remain essential in clinical reporting. Depending on how many patients eventually receive embolization we will plan to compare subjects treated with pre-operative chemotherapy vs. subjects treated with both pre-operative chemotherapy and embolization to better understand the relative contributions of each.

2.3.5 Rationale for chemotherapeutic agents melphalan, topotecan and carboplatin:

Currently, IA chemotherapy for the treatment of intracranial tumors has only been well-established for Rb. Similar to CP tumors, Rb is a primary malignancy most commonly diagnosed in children. We propose to use the same IA chemotherapeutic agents as in Rb consists of melphalan, topotecan and carboplatin. The following are the four reasons to support such approach.

The first reason is based on the potential potency of the chemotherapeutic combination against the invasive nature of ACP and CPC while avoiding off target effects. Melphalan is an alkylating agent that is a nitrogen mustard derivative. It was chosen based on an initial Japanese study that demonstrated its efficacy in cultured human retinoblastoma cells and has since been used as the primary drug in all IA chemotherapy for Rb studies (Abramson et al., 2008; Gobin et al., 2011). Its short half-life of 1.5 hours and its potency against Rb cells make it a great drug choice for IA delivery. Melphalan has been used in combination with topotecan to have a synergistic effect in treating Rb with extensive vitreous seeds. Also, since these two drugs have not been used systemically for either Rb, ACP or CPC, the tumor would not have developed resistance if the patient had previous systemic chemotherapy treatment. Finally, topotecan and/or carboplatin could be added to help with reducing the toxicity of melphalan.

The second reason is based on the well-established toxicity profile of the three-drug combination given intra-arterially in children with Rb (Abramson et al., 2019). Since the introduction of IA chemotherapy for Rb in 2006, there have been multiple reports about the toxicity of the drug combination as it relates to local toxicity, the immune system and growth of children. In most cases, there is little ocular toxicity from IA chemotherapy as much smaller doses of the drugs are used. Carboplatin and topotecan doses are approximately 1/30th of that used systemically. Melphalan is delivered under 0.50 mg/kg. In general, IA chemotherapy related complication rate is reported to be under 5% (Abramson et al., 2016). IA chemotherapy for Rb is also reported to have rare severe adverse effects on the immune system. Neutropenia is a commonly reported side effect but less than 1% of patients require transfusion of any blood product (Dunkel et al., 2014). Finally, the growth of children is not impacted by IA chemotherapy treatment. In fact, children with Rb who received systemic chemotherapy have accelerated growth when they receive IA chemotherapy (Akella et al., 2018).

The third reason is based on the hypothesis that Rb and ACPP/CPC share similar biological mechanisms with respect to their chemosensitivity to drugs. The support for this hypothesis came from the shared combinations of systemic chemotherapy agents used for Rb, ACPP and CPC, which consist of carboplatin, vincristine, etoposide, ifosfamide and cyclosporine. For Rbs, the use of these agents has resulted in 50% of the eyes salvages with 6 to 9 months of treatment. For ACPPs and CPCs, this regimen regardless of whether the patient received radiation therapy had higher 5-year overall survival rate compared with no systemic chemotherapy (Wrede et al., 2009; Wrede, Liu, & Wolff, 2007).

The fourth reason is based on our lab's preclinical data of melphalan, carboplatin and topotecan on cell viability by using the human derived CPC cell line CCHE-45 (This work was done in collaboration

with our co-investigator, Craig Thomas).

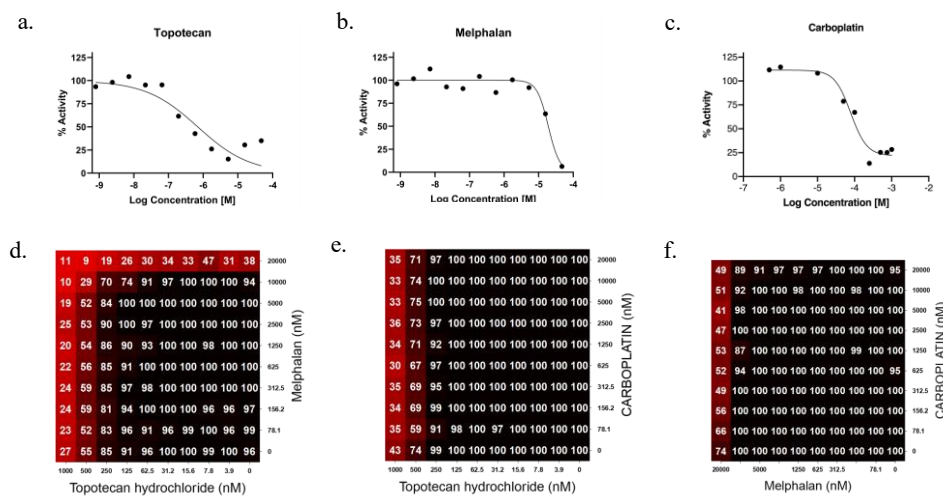


Fig 1. Topotecan, melphalan and carboplatin effectively reduced cell viability on CCHE-45 cell line. (a-c) Cell viability (% activity) is plotted against increased concentration of drugs. (d-f) % of live cells in each specific well of a 10X10 matrix. With increased concentration of drugs across the X- and Y-axis, there was a robust reduction in the % of viable cells.

Melphalan, topotecan and carboplatin was shown to effectively reduced cell viability resulting in IC_{50} of 18 μ M, 200nm, and 78 μ M, respectively (Fig 1, a-c). Drug combination study demonstrated synergistic reductions in cell viability with topotecan and melphalan being the most robust among the three drug combinations (Fig 1, d-f). Combining these reasons, it is plausible to predicate that the new drug combinations would be efficacious when used as IA chemotherapy for the treatment of ACPP and CPC.

2.3.6 Rationale for including children <12 months of age

We believe that including children < 12 months of age is logical and would be valuable in achieving the study objectives. The decision to include this young age in the trial design was based on, (i) our past experience and the established safety profile of the therapeutic approach as well as the procedural safety profile with children <12 months of age, (ii) the prevalence of choroid plexus tumors in infants, (iii) the potential greater benefit of the proposed therapeutic strategy in children < 12 months. We have provided detailed rationale for this approach in the section below.

(i)

- **Toxicity profile of the three-drug combination given intra-arterially in young children.**
The three chemotherapy drugs melphalan, topotecan and carboplatin that we proposed

to administer intraarterially in this protocol are identical to the well-established IA chemotherapy drugs that have been used to treat children <12 months of age with Rb (Abramson et al., 2010; Abramson et al., 2012; Chen et al., 2019; Gobin et al., 2011). Since the introduction of IA chemotherapy for Rb in 2006, multiple studies have examined the toxicity profile of the drug combination as it relates to local toxicity, the immune system and growth of children. In most cases, there is little ocular toxicity from IA chemotherapy as much smaller doses of the drugs are used when compared to systemic injection. Carboplatin and topotecan doses are approximately 1/30th of that used systemically. Melphalan is delivered under 0.50 mg/kg. In general, the IA chemotherapy related complication rate is reported to be under 5% (Abramson et al., 2016). IA chemotherapy for Rb is also reported to have rare severe adverse effects on the immune system. Neutropenia is a commonly reported side effect but less than 1% of patients require transfusion of any blood product (Dunkel et al., 2014). Finally, unlike the effect of systemic chemotherapy on the growth of children, growth was not slowed down in children during the three-drug IA chemotherapy treatment for Rb (Akella et al., 2018; Gobin et al., 2011). In fact, children with Rb who received systemic chemotherapy had accelerated growth when they then received IA chemotherapy (Abramson et al., 2019; Akella et al., 2018).

- **Technological safety of applying the IA procedure in young children is well established.**

The investigators of this study have extensive experience administering IA chemotherapy in young children and have documented its procedural safety based on our institutional studies. Among 292 children with mean age of 14 months (range 1-36 months), IA chemotherapy has resulted in a rate of neurological complications of 0.0%, nonneurological complications of 2.9%, and radiographic complications of 1.3% (Hoffman, Santillan, Rotman, Gobin, & Souweidane, 2014). Our data showed that the rate of complications for IA chemotherapy in young children is comparable to rates reported for older children and lower than rates reported for adults. In addition, our co-investigator of the study, Dr. Gobin, has published numerous studies over the years detailing procedural complications of IA chemotherapy and confirming its safety for children of all ages. For example, one of his publications summarized his four-year experience of managing children with Rb with a median age of 18 months (range 1 mo–21 yr) (Gobin et al., 2011). IA procedural complications have been reported to occur at the femoral puncture site such as hematoma, thromboembolism and limb ischemia, but were considered to be rare incidences and have not been observed in our experience at Weill Cornell.

(ii) Risk of not meeting accrual if infants <12 months of age are not eligible. Detailed age at time of ACPP or CPC diagnosis has been reported by several large clinical studies over the years. While the frequency of children under 1 year of age was not always specified, it was clear that the occurrence of ACPP or CPC in infants <12 months of age is not rare. These examples are demonstrated by studies such as:

- In a total of 14 children with CPC, the median age was 18.6 months (range 1.1-65.3 months), **with 43% <12 months of age** (Lafay-Cousin et al., 2010).
- In a total of 11 children with CPC, the mean age was 22 months (range 1 month-4 years), **with 36% < than 12 months of age** (St Clair et al., 1991).
- In a total of 38 children with choroid plexus tumor, the median age was 22 months, **with 50% <2 years of age** (Pencalet et al., 1998)

- In a total of 7 children with either CPC or ACPP, the median age was 42 months (range 3-190 months), ***with 29% <12 months of age*** (Passariello et al., 2015).
- In a total of 11 children with CPC, the median age was 26 months (range 1 week-7.7 years), ***with 18% <12 months of age*** (Packer et al., 1992).
- In a total of 22 children with CPC, the median age was 26 months and the mean was 33 months (Schneider et al., 2015).
- In a total of 30 children with choroid plexus tumor, the mean age was 26 months (range 15 days-156 months) (Haliasos et al., 2013).
- In a total of 75 CPC cases (based on literature review), the mean age was 26 months (Fitzpatrick et al., 2002).

(iii) The youngest children with ACPP or CPC are most likely to benefit from IA chemotherapy. ACPP or CPC is known for its classic clinical features of voluminous size and vascularity, thus making surgical resection of the tumor extremely high risk in young children with a proportionally smaller circulating blood volume. The hypothetical advantages of the proposed approach is magnified with decreasing age since young children are those at greatest risk of surgery. Given this, the prevalence of ACPP or CPC in children <12 months of age and the established safety of IA chemotherapy in this age group, we propose to enroll young children of any age for this study.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

IA chemotherapy:

The potential systemic and local risks that we can anticipate for IA chemotherapy for ACPP and CPC can be related to system and/or local effects of chemotherapy, and procedural complications.

Systemic complications of IA chemotherapy include neutropenia, which is typically mild and rarely requires an intervention. Bronchospasm is a potentially serious complication that occurs in 8.3% of procedures and is easily reversed by the administration of epinephrine. Iodine allergy is rare in children. Ischemic and hemorrhagic stroke are possible with IA chemotherapy but have not been observed in our experience at Weill Cornell. There has been 1 report of a vascular spasm that occurred during cannulation of an anomalous internal carotid artery uneventfully (Shields et al., 2011).

Procedural complications occurring at the femoral puncture site such as hematoma, thromboembolism, and limb ischemia are possible, especially with repeated intervention. Among the more than 100 cannulations studies published, only 1 groin hematoma (Peterson et al., 2011) and 1 transient femoral artery occlusion have been reported. Ischemic and hemorrhagic stroke are possible with IA chemotherapy but have not been observed in our experience at Weill Cornell. Our institutional experience in infants (< 3 years) has resulted in a rate of neurological

complications of 0.0%, nonneurological complications of 2.9%, and radiographic complications of 1.3% (Hoffman et al., 2014).

Risks related to pregnancy and sexual activity while being treated by the chemotherapy drugs:

The chemotherapy drugs that will be used for this study can cause fetal harm. Women of childbearing potential should use highly effective contraception during and for at least six months after treatment of the drugs has been stopped. Men should use contraception during and for 3 months after treatment of the drugs has been stopped. Serum pregnancy test will be part of the physical exam that will take place during visits of the study. Women of childbearing age who became pregnant or are lactating will be excluded from the study.

IA embolization:

Potential risks associated with IA embolization include stroke from the unintended occlusion of embolic material that can result from reflux of liquid embolic material and small particle size.

2.4.2 Known Potential Benefits

IA chemotherapy:

By adopting the well-established pre-operative IA chemotherapy and establish it as a pre-operative strategy for ACP and CPC, the potential benefits can include the following:

- (i) IA chemotherapy decreases systemic toxicity and dose-limiting side effects. As shown by Rb, treatment with IA chemotherapy uses far less chemotherapy than systemic chemotherapy and has eliminated the need for external beam irradiation. Since there is less dosage of chemotherapy agents required by the IA approach, less systemic toxicity is involved. The doses of carboplatin and topotecan used in IA chemotherapy for Rb are reported to be approximately 1/30th that used systemically (Abramson et al., 2019). With that small dosage, animal studies showed the drug levels in the eye were 100 times higher compared with that obtained with systemic delivery (Francis et al., 2013).
- (ii) An enhanced reduction in tumor volume and vascularity compared with systemic chemotherapy with shorter treatment period. For example, compared with radiation or multi-agent systemic chemotherapy, IA chemotherapy for Rb resulted in more advanced eyes salvaged (Chantada & Schaiquevich, 2016). Mean number of treatments is just over 3 monthly infusions, but success has been obtained with as little as one IA chemotherapy.
- (iii) IA chemotherapy is considered a minimally invasive procedure.

IA embolization:

IA embolization is an adjunctive procedure that has been done pre-operatively in various types of tumors for over 3 decades. In recent years, pre-operative embolization has been done in children diagnosed with CPC. Pre-operative IA embolization followed by 2nd look surgery of CPCs reduced the amount of intra-operative blood loss, resulted in higher rates of total resection and lower operative morbidity and mortality (Haliasos et al., 2013; Slater et al., 2016; Wang et al., 2013).

3. Study Design

3.1 Overall Design

This is a single-arm, single site, open-label, pilot study with an intervention of pre-operative intra-arterial chemotherapy for newly diagnosed, residual or recurrent ACPP or CPC in children prior to 2nd look surgery.

We hypothesize that pre-operative super-selective IA chemotherapy for newly diagnosed, residual, or recurrent ACPP or CPC in children/adults is safe. We further hypothesize that IA chemotherapy for ACPP and CPC is feasible and will result in decreased tumor volume and vascularity (i.e. perfusion). This strategy may ultimately potentiate the goals of 2nd look surgery.

Upon screening and enrollment, all patients will have a MRI assessment. Prior to IA-chemotherapy an assessment to identify suitable vasculature will be conducted. Any technical failures during assessment (e.g. catheter cannot reach close to the site of the tumor, etc) will be considered angiographic screen failures. All eligible patients that have a successful angiogram assessment will then have a single dose of IA chemotherapy, followed by a MRI assessment weeks later to assess the efficacy of IA chemotherapy administration. Depending on the patient's response to IA chemotherapy, the patient may or may not be considered for second-look surgery. At the discretion of the neurosurgeon, the need for embolization prior to 2nd look surgery will be decided.

All patients will have a follow up visit 6 (4-6 weeks post visit 5) and will be followed for up 1 one year after their last visit to assess overall survival.

3.2 Scientific Rationale for Study Design

This protocol qualifies for phase I clinical trial based on the design of a small number of patients for whom other standard treatment could not be applied or have failed. Patients who participate in this phase I trial are the first to receive pre-operative IA chemotherapy prior to 2nd look surgery. The chemotherapeutic agents melphalan, carboplatin and topotecan will be given. The primary goal of this phase I trial is to determine the safety of a single dose of IA chemotherapy for newly diagnosed, residual, or recurrent ACPP and CPCs prior to 2nd look surgery.

*Please see detailed scientific rationale for study design written on section: 2.3 Rationale.

3.3 Justification for Dose

The doses for IA chemotherapy rely on local as well as systemic effects. For local toxicity, the size of cerebral vascular territory is the major factor for deciding the dose. This is inspired by work from Gobin et al. 2001, which found that toxicity from IA chemotherapy can be minimized if dose is adjusted for the size of domain infused. The dose is also calculated so that it is below the threshold for systemic toxicity.

Systemic toxicity: for melphalan, systemic toxicity occurs for dosages $> 0.5\text{mg/Kg}$, for carboplatin, it is 18.5mg/Kg and for topotecan 2mg/m^2 . So the total dose of these drugs should not be over the limits of systemic toxicity. In IA chemotherapy for retinoblastoma, systemic toxicity is the limiting factor for melphalan and topotecan.

Local toxicity: it depends on the arterial territory. The size of the artery where the injection is done will be compared with the size of the ophthalmic artery, because we have extensive experience of IA chemotherapy of these drugs in the ophthalmic artery and by analogy, we estimate that local toxicity in the choroidal arteries will be similar to (or less than) the ophthalmic artery. In the ophthalmic artery, we have seen ophthalmic toxicity with the following dosage: for melphalan if $>7.5\text{ mg}$, for carboplatin if $>50\text{ mg}$, for topotecan no toxicity observed with a dose of 2 mg . In IA chemotherapy for retinoblastoma, local toxicity is the limiting factor for carboplatin.

Systemic and local toxicity calculation for IA chemotherapy for ACPP and CPC:

For melphalan and topotecan, systemic dosage limit will be taking into consideration when infusing the drugs. If multiple arteries are identified and needed to be infused, systemic dosage limit ($> 0.5\text{mg/kg}$ for melphalan and $>2\text{mg/m}^2$ for topotecan) will be divided per the arteries that will be infused. In terms of local toxicity, the maximal dose that can be safely injected into an artery will be adapted to the size of the artery such that an artery the size of the ophthalmic artery would not receive more than their local toxicity dosage limit of 7.5 mg for melphalan and 2mg for topotecan.

For carboplatin, where systemic toxicity dosage limit is high (18.7mg/kg), the limiting factor will most likely be local toxicity dosage limit ($>50\text{mg}$). Therefore, the dose infused into each artery catheterized will be dosed proportionately to the size of the artery, such that 50 mg would be given in an artery the size of the ophthalmic artery (and 25 mg if the artery is half the size, or 100 mg if double the size of the ophthalmic artery, etc..). However, if several arteries are to be infused, the total carboplatin dose will not be higher than systemic toxicity dosage limit of 18.7 mg/kg .

In summary,

- The maximum total dose of melphalan that can be applied is 0.5mg/kg , of which a maximum of 7.5 mg may be administered into one individual artery.
- The maximum total dose of topotecan that can be applied is 2mg/m^2 , of which a maximum of 2mg may be administered into one individual artery.
- The maximum total dose of carboplatin that can be applied is 18.7 mg/kg , of which a maximum of 50 mg may be administered into one individual artery.

IA chemotherapy doses in ACPP and CPC:

For ACPP or CPC, arteries significantly supplying the tumor will be catheterized and infusion of chemotherapy will be performed. Systemic and local toxicity dosage limit will be taken into account for all three drugs to ensure the combined dosage to all arteries do not exceed the toxicity limit. Factors that determine drug dosage are based on the technique developed by Gobin et al. 2001 and Dr. Gobin's extensively experience on IA chemotherapy for retinoblastoma. Dosage for IA chemotherapy will be given based on, (1) the size of the territory infused- that is, the size of the tumor, and (2) dose fractionation after examining the angio-anatomy of the choroidal artery and its branches. Unfortunately, there is no technique to quantify bloodflow in these small vessels and therefore it cannot be used as a factor for dosage.

Final concentrations of the drugs to be used for infusion are approximated to be: melphalan 0.5mg/ml, topotecan 0.2mg/ml and carboplatin 5 mg/ml. The total volume of each drug is approximately 10 ml but if the drugs have to be injected in several arteries the volume injected in each artery will be less, so the time of injection will be less. Therefore, each of the chemotherapy drugs will be diluted with saline to a 2-ml to 10-ml final solution and injected in a pulsatile fashion consecutively over 2 min to 10 min. For example, if we identify that the vascularization to one tumor comes at 70% from the anterior choroidal artery and at 30% from a posterior choroidal artery, and if the injection volume of the three drugs is 30 cc, we will catheterize the anterior choroidal artery, inject the 3 drugs successively for a volume of 21 cc in the anterior choroidal artery in 21 minutes, then catheterize the posterior choroidal artery and inject successively the three drugs for a volume of 9 cc in 9 minutes. If more than one artery is identified and is required for IA chemotherapy, catheterization of the second artery and infusion of drugs to the second artery will start after the previous artery is completed.

Please note that the drug concentrations and volumes proposed here are estimated based on previous experience with IA chemotherapy for Rb. Our experience with IA chemotherapy for Rb has provided an important reference for this study, however, the exact concentration and volume may need to be adjusted during the procedure after assessment of the size of cerebral vascular territory, the size of the tumor domain and the angio-anatomy of the choroidal artery and its branches.

Please note that we cannot mix the three drugs and we have to inject them successively. We plan to use the same sequence of chemotherapy drug administration for all study subjects. We do not intend to record the time of infusion of each drug as this would be a departure from our usual and customary method of IA drug administration and nor has there been any past recognition of tolerance being time dependent. While the simultaneous administration of drugs is appealing as it relates to a shortened time of infusion there are two guiding rationales to use sequential administrations. First, the treatment time of 30 minutes is not excessive and has been demonstrated as safe by our group in numerous infants over many years. More importantly, drug-drug interactions, drug precipitation, toxicity profiles, solubility, and bioavailability could all be altered and are unknown with mixing these drugs.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the **Schedule of Assessments (SoA), Section 6.1**. The end of the study is defined as completion of the last visit or procedure shown in the SoA for every subject in the trial.

4. Subject Selection

4.1 Study Population

Subjects of any age with newly diagnosed, residual, or recurrent ACPP or CPC, who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Subjects with a histologically confirmed diagnosis of ACPP or CPC that is newly diagnosed, residual or recurrent.
2. Subjects must have a Karnofsky or Lansky Performance Score $\geq 60\%$ assessed within two weeks prior to enrollment. Karnofsky is used for patients ≥ 16 years and Lansky for those < 16 .
3. Subjects must have normal organ and marrow function documented within 14 days of enrollment as noted below:
 - a. Absolute neutrophil count $\geq 1,000/\mu\text{L}$
 - b. Platelets $\geq 100,000/\mu\text{L}$ (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment)
 - c. Hemoglobin $\geq 8\text{ g/dL}$ (may receive PRBC transfusions)
 - d. Total bilirubin < 1.5 times upper limit of normal for age
 - e. AST (SGOT)/ALT (SGPT) $< 2.5 \times$ institutional upper limit of normal for age
 - f. Creatinine clearance or radioisotope GFR $\geq 70\text{ ml/min/1.73m}^2$ or a serum creatinine WNL for age as determined using the Schwartz formula.³⁶
 - g. Sodium, Potassium, Calcium and Magnesium $< 1.5 \times$ institutional ULN
 - h. Albumin $\geq 3\text{ g/dL}$
4. Subjects who are receiving dexamethasone must be on a stable or decreasing dose for at least 1 week prior to enrollment.
5. Subjects with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment.
6. If the subject has any of the following therapies, must be at least:
 - 4 weeks post-focal RT (radiation therapy), 3 months post-CSI (craniospinal irradiation)
 - 4 weeks post-myelosuppressive chemotherapy (if post-nitrosoureas, must have 6 weeks therapy)
 - 4 weeks post-monoclonal antibodies
 - 1 week post-targeted therapy
7. If subject has received any previous treatment, all treatment related toxicities should have recovered to $< \text{grade } 2$
8. Subject or parent must sign a written informed consent document according to institutional guidelines.

4.3 Exclusion Criteria

1. Females who are pregnant or lactating.
2. Subjects with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) likely to interfere with the study procedures or results.
3. Subjects who are receiving any other anticancer or investigational agents.
4. Subjects with uncontrolled seizures.
5. Subjects receiving enzyme inducing anticonvulsants.

6. Subjects with other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome) including heart failure that meets New York Heart Association (NYHA) class II or above.
7. Subjects who have had an allogenic bone marrow transplant < 6 months prior to enrollment or an autologous bone marrow/stem cell transplant < 3 months prior to enrollment.
8. Subjects with multifocal disease or disease that has been disseminated will not be eligible for this study. They will undergo systemic chemotherapy and their disease will be further evaluated prior to be eligible for 2nd look surgery.
9. This study will only enroll subjects with ACPP or CPC and will not enroll subjects with choroid plexus papilloma (CPP). ACPP or CPC subjects with symptomatic hydrocephalus will not be eligible for this study. These subjects will have to be treated for their hydrocephalus and be re-evaluated according to our eligibility criteria in order to be enrolled.

4.4 Lifestyle Considerations

During this study, participants are asked to:

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] 1 day before the start of angiography or any radiographic diagnosis.
- Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of each dosing session until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- Abstain from alcohol for 24 hours before the start of each dosing session until after collection of the final PK and/or pharmacodynamic sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.
- Abstain from strenuous exercise for 2 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Subjects will be recruited by the PI in an outpatient clinic setting. Subjects who may meet eligibility criteria will be recruited regardless of gender, race and ethnicity. Up to 12 subjects will be screened in order to reach the enrollment goal of 6 for the treatment plan. The only site that will be recruiting is Weill Cornell Medicine.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

Table 3. Schedule of trial events

	Screening	Visit 1 (Day1)	Visit 2 (V1 + 1- 14 days)	Visit 3 (V2 + 1 week ± 3 days)	Visit 4 (V2 + 2 weeks ± 3 days)	Visit 5 (V2 + 4-6 weeks ± 7 days)	Visit 6 Follow-up visit (V5 + 4-6 weeks)	Survival Follow Up (V6 + 1 year ± 2 months)
MRI		X				X		
Pre-operative IA chemotherapy			X					
+/-pre-operative embolization ^A						X		
2 nd look surgery ^A						X		
Disease confirmation (Pathology report review)	X							
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	X		X			X	X	
Physical exam	X			X	X		X	
Karnofsky/ Lansky performance score	X			X	X		X	
Vital signs	X		X	X	X	X	X	
Height and Weight	X						X	

Labs ^B	X			X	X		X	
Adverse event evaluation			X	X	X	X	X	
Outcome evaluation			X ^C			X ^{D, E, F}		
Phone Call for Overall Survival								X

Details of the procedures:

A. To occur at the discretion of the treating physician

B. Labs include CBC with differentials (CBC + Diff), Basic Metabolic Panel (BMP) plus magnesium (Mg) and Hepatic panel (HP). Serum pregnancy test for women of childbearing age

C. Angiographic procedural success determined by assessing vasculature suitable for IA therapy; technical failures, e.g. catheter cannot reach close to the site of the tumor, etc. will cause for subjects to be deemed screen failures

D: tumor size/volume, cellularity, and vascularity (perfusion) measurements assessed on MRI

E: measurement of EOR, CBL, % blood loss

F: pathology correlates of vascularity and tumor viability (tissue will be collected immediately after surgical resection when possible.)

6.1.1 Screening Visit for study eligibility

- Informed consent
- Demographics
- Medical history
- Medication history
- Physical exam
- Vitals
- height and weight
- Karnofsky/ Lansky performance score
- Bloodwork
- Concomitant medications
- Confirmation of newly diagnosed, residual or recurrent ACPP or CPC by pathology report

6.1.2 Treatment Phase

6.1.2.1 Visit 1 (Day 1)

- MRI baseline measurement

6.1.2.1 Visit 2 (V1 + 1-14 days)

- Pre-operative IA chemotherapy
- Vitals
- Concomitant medications
- Adverse event evaluation
- Outcome evaluation (as described in Table 3)

6.1.2.3 Visit 3 (V2 + 1 week \pm 3 days)

- Vitals
- Physical exam
- Karnofsky/ Lansky performance score
- Bloodwork
- Adverse event evaluation

6.1.2.4 Visit 4 (V2 + 2 weeks \pm 3 days)

- Vitals
- Physical exam
- Karnofsky/ Lansky performance score

- Bloodwork
- Adverse event evaluation

6.1.2.5 Visit 5 (V2 + 4-6 weeks \pm 7 days)

Visit window (1 week)

- MRI (to assess IA efficacy)
- Pre-operative embolization
- 2nd look surgery
- Outcome evaluation (as described in Table 3)
- Adverse event evaluation
- Vitals
- Concomitant medications

6.1.3 Follow-up Phase

6.1.3.1 Visit 6 (V5 + 4-6 weeks)

- Concomitant medications
- Physical exam
- Karnofsky/ Lansky performance score
- Vitals
- Height and weight
- Bloodwork
- Adverse event evaluation

6.1.4 Follow-up survival (V6 + 1 year \pm 2 months)

- Phone call for overall survival

7. Study Intervention

7.1 Study Intervention/Device Description

Description of Chemotherapeutic Agents

Melphalan is a mustard gas derivative and alkylating agent that has been an FDA approved chemotherapy since 1964. A single dose clear glass vial containing 50 mg of freeze-dried melphalan and one clear glass vial of 10mL sterile diluent will be utilized. Storage will be at room temperature (20-25°C) avoiding light exposure. Vial will be shaken vigorously until solution is clear and colorless. The reconstituted solution is stable for 1 hour at 25°C or 24 hours at 4°C. The reconstituted solution will be further diluted to a final concentration of 0.5mg/ml in the angiography suite by the neurointerventionalist before use and the diluted solution is stable for 4 hours, including infusion time, at 25°C or 24 hours at 4°C. Precautions are needed in patients with bone marrow suppression or renal failure (BUN>30mg/dL), both of which will be screened for in the present study. Contraindications of melphalan include patients that have demonstrated hypersensitivity to melphalan, severe bone marrow depletion, and patients whose tumors have demonstrated resistance. Guideline for the currently used melphalan drug is taken from the manufacture's website: <https://evomela.com/evomela-stability/>. This guideline is also consistent with NYP guidelines, <https://infonet.nyp.org/pharmacy/PharmacyM/antineoplasticdilutiontable.pdf>.

Carboplatin is a platinum-based chemotherapy, which as a class, is used to treat almost half of all patients with cancer. The mechanism of action is mainly via crosslinking of purine bases which interrupt DNA repair and synthesis. It will be supplied as a 10mg per mL of sterile water/mannitol solution in clear glass vials of either 5mL, 15mL or 45mL. Reconstitution is therefore not needed, but dilution to the appropriate dose will be performed in the angiography suite by the neurointerventionalist who will add the appropriate amount of NS to a final concentration of 5 mg/ml before using. Carboplatin vials will be stored at 25°C and protected from light. Vials are stable until date labeled on manufacture packaging. Diluted solutions are stable 9 days after dilution when store at 25°C. Precautions are needed in patients with bone marrow suppression or renal failure, both of which will be screened for in the present study. Contraindications of carboplatin include patients that have demonstrated hypersensitivity to carboplatin, severe bone marrow depletion, or significant bleeding.

Topotecan is a topoisomerase 1 inhibitor which inhibits a cell's ability to separate DNA for replication. Topotecan is supplied as 4mg of yellow-green powder lyophilized and buffered in a single dose clear vial for reconstitution. It is reconstituted with 4 mL of sterile water which is injected into the single dose vial and vigorously shaken. Once in solution, it can be further diluted with either 0.9% saline or D5W in the angiography suite by the neurointerventionalist to a final concentration of 0.2 mg/ml. Both powder and solution will be stored at 25°C and protected from light. Reconstituted solution is stable for 28 days at 25°C and the further diluted solution is stable for 24 hours at 25°C or 7 days at 4°C. Precautions are needed in patients with bone marrow suppression. Contraindications of topotecan include patients that have had a past hypersensitivity reaction and patients with severe myelosuppression.

All three chemotherapies are toxic compounds and will be handled with caution. All are dermal irritants and can cause eye damage if accidental contact with the eye is made. Any handling of the agents will be done in a closed system drug-transfer device (CSTD) to avoid contact with the agents.

Description of IA Administration Procedure

The procedure is done under general anesthesia as an outpatient at a catheterization laboratory or interventional suite. Patients are pre-treated with heparin (50-80 IU/kg) to prevent thrombotic events. The femoral artery ipsilateral to the target artery is used as access and a 4-French arterial sheath is inserted into it. The angiogram shows the vascularization of the tumor and the neurointerventionalist decides the arteries that should be catheterized and injected with the chemotherapy drugs. We expect that the choroidal arteries (anterior, posterior medial and posterolateral) will be the main arterial feeders although in large tumors cortical arteries could also participate to the tumoral vascularization. Under road-mapping fluoroscopic guidance, a senior interventional neuroradiologist guides the microcatheter to the target artery. Once the target artery is reached, serial angiograms are taken to evaluate and confirm the cerebral vasculature. When angiogram confirms correct placement and stability of the microcatheter, selected chemotherapies are infused.

Following common practice with IA chemotherapy in retinoblastoma, all doses of chemotherapies will be prepared in the angiograph suite by the neurointerventionalist. Each of the chemotherapy drugs will be diluted with saline to its final concentration in a 2-ml to 10-ml solution and injection in a pulsatile fashion consecutively over 2 min to 10 min. If more than one artery is identified and is required for IA chemotherapy, catheterization of the second artery and infusion of drugs to the second artery will start after the previous artery is completed.

After the IA administration procedure

Once all arteries have been infused, a repeat angiogram is done to exclude thrombotic events and the catheter is withdrawn. After the procedure, patients are monitored overnight in the PICU or outpatient unit and their vital signs are continuously checked. Finally, the neurointerventionalist ensures that there are no adverse events associated with the procedure and patients are then discharged.

See section 3.3 (Justification for Dosage) for detail rationale for dosage for multiple arteries.

7.2 Availability, Acquisition, and Accountability

Melphalan, topotecan, and carboplatin will be supplied by NYP pharmacy as per retinoblastoma (ophthalmic oncology) protocol.

7.3 Product Storage and Stability

All three agents can be kept at room temperature (20-25°C) and will be protected from light in a dark and dry place.

The following stability information is from the “Antineoplastic & Select Non-Antineoplastic Reconstitution/Dilution/Filtration Data Table” procured by NewYork-Presbyterian Hospital. For melphalan, the reconstituted solution is stable for 1 hour at 25°C or 24 hours at 4°C. The diluted solution is stable for 4 hours, including infusion time, at 25°C or 24 hours at 4°C. For carboplatin, diluted solutions are stable 9 days after dilution when stored at 25°C. And for topotecan, the reconstituted solution is stable for 28 days at 25°C and the further diluted solution is stable for 24 hours at 25°C or 7 days at 4°C.

7.4 Preparation

Melphalan will be reconstituted by injecting 10mL of supplied diluent into the vial of melphalan powder using a sterile needle. Vial will be shaken vigorously until solution is clear and colorless. The reconstituted solution of 5mg/mL will be further diluted to a final concentration of approximately 0.5mg/ml in a volume range between 2-10 ml in single use vial and shake for 1-2 minutes before infusion.

Carboplatin is supplied in 10mg/mL and will be diluted to final concentration of approximately 5mg/ml by adding the calculated volume of D5W solution or NS into the vial via sterile needle. Once additional volume is added, the solution will be shaken 1-2 minutes to ensure proper dispersion of chemicals.

Topotecan is reconstituted with 4 mL of sterile water which is injected into the single dose vial and vigorously shaken. Once in solution, it will be further diluted with either 0.9% saline or D5W via sterile needle to a final concentration of approximately 0.2 mg/ml and subsequently shaken for 1-2 minutes.

7.5 Dosing and Administration

Artery Selection

Each enrolled patient will receive IA chemotherapy after a screening visit and an MRI-based angiographic assessment of tumor domain. The specific arteries for infusion will be decided by (1) tumor domain as evidenced by MRI, defined here as areas of gadolinium contrast enhancement with T1-weighted images and/or areas of high signal intensity with T2-weighted images and (2) information about individual arterial anatomy received from both the angiographic assessment and knowledge of common arterial anatomy. The arteries selected will be the ones that feeds most or all the tumor(s) and can be selectively catheterized.

Dose

As in advanced retinoblastoma, all patients will receive a combination of melphalan, carboplatin and topotecan. (Abramson et al., 2008; Manjandavida, Stathopoulos, Zhang, Honavar, & Shields, 2019). Melphalan will not be given if there is a history of hypersensitivity to melphalan.

Dosage:

The three drugs are diluted to the final approximate concentrations:

Melphalan: 0.5 mg/ml

Carboplatin: 5 mg/ml

Topotecan: 0.2 mg/ml

Each drug is diluted in a volume ranging approximately 2-ml to 10-ml. Factors that determine drug dosage are based on the technique developed by Gobin et al. 2001 and Dr. Gobin's extensively experience on IA chemotherapy for retinoblastoma. Dosage for IA chemotherapy for ACPP and CPC will take into consideration: (1) the estimated systemic and local toxicity limit for each drug, (2) the size of the territory infused- that is, the size of the tumor, (3) dose fractionation after examining the angio-anatomy of the choroidal arteries and its branches, and (4) the use of pulsatile injection technique to ensure homogenous delivery of drugs.

Rationale for current approach to IA chemotherapy drug dosage:

To further support our current approach to IA chemotherapy drug dosage, we carefully reviewed existing literature on IA chemotherapy dosage approaches for brain tumors and made the following summary. **First**, please note that we cannot angiographically measure blood flow in these small vessels, which is why we relied on our previous experience with intra-arterial chemotherapy in the brain and the eye. **Second**, the effectiveness of using our current approach of spatial dose fractionation based on angio-anatomy of the vessels for IA chemotherapy has been well demonstrated for brain tumors (Burkhardt et al., 2011; Gobin et al., 2001). In multiple analyses involving 117 progressive or recurrent malignant brain tumor patients (with a mean age of 48 years; age range between 5-77 years), spatial dose fractionation predicted drug toxicity, whereas body weight or body surface area dose did not. Furthermore, it has also been noted that cerebral weight, volume, and blood flow differ little among individuals (Gobin et al., 2001; Shapiro & Green, 1987). **Third**, attempts of using blood flows to guide IA chemotherapy dosage were made in the past with little success. For example, one study attempted to measure the blood flows in the major cerebral arteries (middle cerebral, posterior cerebral, anterior communicating arteries) by measuring the arterial velocities and cross-sectional size. Arterial blood velocities were measured with intravascular Doppler and with trans-cranial Doppler, while the arterial cross-sections were measured on MRI or during the angiograms. However, there was high interobserver variability with intra-arterial as well as trans-cranial Doppler measurements. The cerebral vessels had a diameter of one to three millimeters and their measurements on MRI or on angiogram were not very precise. It was concluded that the blood-flow measurements had a margin of error of at least 100% and were time consuming (Burkhardt et al., 2011; Cloughesy et al., 1997).

See section 3.3 (Justification for Dosage) for detailed rationale and dosage of drugs for infusion.

Dosing Delays/Dose Modifications

- Dosage modifications are subject-dependent, and a justification is provided in section 3.3 (Justification for Dosage).

7.6 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

7.7 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), the protocol regimen may continue as specified above until the regimen is complete, or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

7.8 Duration of Follow Up

Subjects will be followed for __1 year____ after removal from study or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.9 MRI Exams

Subjects will undergo a baseline MRI exam within 2 weeks (0-14 days) of initial intra-arterial chemotherapy. Baseline and subsequent MRIs will follow a standardized imaging protocol with maximum duration of 55 minutes. Sedation for MRI exams will be provided by anesthesia as necessary per routine clinical care. Suggested sequence acquisition includes: pre-contrast axial diffusion, QSM/SWI/MAG, sagittal 3D T1, axial T2, arterial spin labeling (ASL) perfusion, and intravoxel incoherent motion (IVIM); post-contrast 3D sagittal T2 FLAIR with fat saturation, and sagittal 3D T1 post-contrast sequences. 3D time-of-flight MR angiography may be added for MR-based angiographic assessment and 3D T1 MPRAGE/SPGR sequence may be added for pretreatment planning, as clinically indicated. Sequences may be added or subtracted by the protocoling radiologist. All MR exams will be interpreted by a board-certified neuroradiologist.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

If a subject needed to be discontinued from angiography due to screen or technical failure, the subject would not participate in the treatment plan. The subject would be not be counted as one out of the total of 6 subjects in the treatment plan but would be included for angiography feasibility endpoint analysis.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants and/or their parent(s)/legal guardian(s) are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive pre-operative IA chemotherapy or second-look surgery 5 -10 weeks post angiography assessment.
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up after several attempts to contact them and/or their parent(s)/legal guardian(s) to schedule study visit.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not Applicable

10. Response Criteria

10.1 Radiographic assessment

10.1.1 Tumor volume

A board-certified neuroradiologist will record tumor size at baseline (pretreatment) and follow up response assessment MRI exams. The Children's Oncology Group (COG) guidelines will be primarily utilized as the radiographic response criteria: tumor size and volume (cross-product of longest tumor dimension and its perpendicular on the axial plane and length perpendicular to the plane of axial measurement), excluding portions of cysts/necrosis. COG methodology is detailed in Appendix I. Enhancing 3-D tumor volumes will secondarily be determined in a semi-automated manner using FDA-approved software (Olea v3.2 and/or GE Advantage Workstation v4.6) to select a seed voxel at the center of enhancing tumor and expanding the region of interest to include voxels of similar signal intensity. Areas of hemorrhage, cysts, and necrosis are excluded. Manual editing will be performed to include or exclude voxels as necessary. Both manually calculated COG-based tumor volume and semi-automated volume will be recorded.

10.1.2 Tumor vascularity (perfusion)

Pathology correlates of vascularity will be reported for resected tumor as detailed in section 10.3. MR pulse sequences will be utilized to assess tumor vascularity in-vivo if imaging time permits on baseline and follow-up MRIs using arterial spin labeling (ASL) and/or intravoxel incoherent motion (IVIM) technique, as determined by the radiologist. These sequences provide quantitative measures of perfusion which correlate with histopathologic vascularity (Kikuchi et al., 2019; Noguchi et al., 2008).

10.2 Surgical

Calculated blood loss (CBL) will be obtained by the following formula: $CBL = RBC + (EBV) \times (HCT_{preop} - HCT_{postop})$ where RBC= volume of transfused red blood cells, EBV= estimated body volume, calculated as 80mL/kg, and HCT= hematocrit values received before and after surgery respectively.

Percent blood loss will be calculated as: $\frac{CBL}{EBV} \times 100$

Extent of resection (EOR) will be calculated as the difference between pre-operative and post-operative tumor volumes, which will be obtained as detailed in 10.1.1. A gross total resection is defined as a no visible tumor on neuroimaging and a near-total resection is defined as residual tumor volume that is less than 5% the preoperative volume. Subtotal resection is defined as

residual tumor volume more than 5% the preoperative volume (Schneider et al., 2015).

10.3 Pathology

The following neuropathological parameters will be recorded by a board-certified neuropathologist for each tumor resection. These will be assessed by examination of routine formalin fixed paraffin embedded sections:

- The presence or absence of sheet-like growth
- The presence or absence of brain parenchymal invasion.
- The presence or absence of necrosis, semi-quantitated to the nearest 10% increment as a percentage of the sampled surface area of tumor tissue.
- The presence or absence of p53 immunohistochemical labeling.
- The presence or absence of TP53 mutation along with variant allele frequency as assessed by the Oncomine Comprehensive Panel v2 (or a similar next generation sequencing targeted panel).
- The extent of vascularity in the resected tumor will be calculated as a percentage of nuclei labeling positively for ERG (avian v-ets erythroblastosis virus E26 oncogene homolog) by immunohistochemical staining over total hematoxylin counter-stained nuclei in 4 representative 400X fields of viable tumor. ERG is an ETS (erythroblast transformation specific)-related gene. It is a member of the ETS family of transcription factors.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified

persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

For participants who are ≥ 18 years but do not have the capacity to consent, legally authorized representative will sign the approved informed consent. Similarly, if a participant is unable to provide assent, then this will be documented verbally whenever possible or documented that assent cannot be obtained. However, consent will be obtained from their legally authorized representative. Capacity to consent/assent will be determined based on their medical chart review and their care physician input. The research team will follow clinical care team guidelines as the research is intertwined with clinical care.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must be approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

Parental permission, child assent and adult consent process will be available in-person or remote using DocuSign.

In-person Consent

The study will be explained to the subject in the outpatient and inpatient clinics of NewYork Presbyterian Hospital-Weill Cornell Medical College and any questions the subject has will be answered to the subject's satisfaction. Written informed consent will be obtained from the subject and a signed copy will be given to the subject.

Remote Consent

Participants will be consented remotely using an electronic version of the informed consent form that follows federal, state, and local regulations, as applicable. We will implement the following procedures for electronic informed consent.

The informed consent document(s) will be sent to the subject or their Legal Authorized Representative (LAR), if applicable, via secure email sent by DocuSign prior to the scheduled consent discussion. The subject or LAR will be asked to review the consent document prior and during the consent discussion with a study staff member via phone or approved teleconferencing service (i.e., Zoom). The study staff member will confirm the subject or LAR has read and has the capacity to appreciate all aspects of the information presented in the consent process for the research study. The subject or LAR will be encouraged to ask questions. If agreeing to participate,

the subject or LAR will sign the consent form using electronic informed consent (eConsent) via DocuSign. A computer, tablet or touch screen phone will be used to capture digital signatures. If applicable, the person conducting consent will also sign the electronic informed consent (eConsent) document in a contemporaneous manner. Subjects will be provided with a digital copy of the completed form via email.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoint

The primary endpoint is to establish safety of the IA chemotherapy in ACPP and CPC.

Other endpoints of interest are:

- Rate of angiographic procedural success (screen failures, technical failures, etc.)
- Measurements of EOR, CBL, % blood loss
- Degree of volumetric tumor reduction based on MRI
- Pathology correlates of vascularity and tumor viability

12.2 Sample Size/Accrual Rate

N=6 (for the treatment plan), accrual rate 1 subject/4 months

12.3 Analysis of Endpoints

12.3.1 Analysis of Primary Endpoint

The treatment will be considered safe in this patient population if 1 or fewer has a severe adverse event (SAE), grade 4 or greater, (as defined in section 13.2) are reported as at least possibly related to the intervention. A SAE is any untoward medical occurrence that results in death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. The number (percent) of patients with a SAE will be determined. The types of SAE will be described for each patient.

12.3.2 Analysis of Secondary Endpoints

- The number and proportion of angiographic procedural success (screen failures, technical failures, etc.) will be reported.
- The number and proportion of patients with a tumor volume and vascularity reduction response will be reported.
- Measurements of EOR, CBL, % blood loss will be done. These measures will be summarized with means, median, and standard deviations. The values will be displayed as a dot plot.
- Pathology correlates of vascularity and tumor viability will be reported. Both the distribution of values will be graphed and summarized with summary statistics. Scatterplots will be used to summarize the relationship between values. No hypothesis testing will be done given the small sample size.

12.4 Reporting and Exclusions

12.4.1 Evaluation of Toxicity

All subjects who underwent IA chemotherapy will be evaluated for adverse events from the time of treatment initiation until 60 days post-procedure.

12.4.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received IA chemotherapy.

12.5 The stopping rule for this study

The stopping rule describes the situation under which the study may stop early. The study will be closed or stopped when we detect for the first time, two patients who have a SAE, grade 4 or greater, are reported as possibly related to the intervention. SAE is defined as any untoward medical

occurrence that results in death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition (as described in section 13.2).

13. Adverse Event Reporting Requirements

13.1 Adverse Event Definition

An **adverse event** (AE) is any undesirable, noxious, or pathological change, compared to pre-existing conditions, that occurs to a subject during a clinical research study or the follow-up period, whether or not it is considered to be related to the study intervention, test drug or surgical procedure. Adverse experiences include:

- Suspected adverse drug reactions.
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of research study medication.
- Other medical events, regardless of their relationship to the test drug, such as injury, surgery, accidents, extensions of symptomatology, or apparently unrelated illnesses.

13.1.1 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

- **Attribution** of the AE:
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

Evaluating Adverse Experiences: The investigator will determine the seriousness, intensity, and causality of an adverse event based on the grading definitions found in the CTCAE version 4.0 or higher.

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject’s daily activities

Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject’s usual daily activity, and require systemic drug therapy or other treatment

Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death

Grade 5 (Death related to AE) – experiences which result in subject death

13.1.2 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject’s research chart.

All adverse experiences (including SAEs) are to be accurately recorded on the Adverse Experience page of the patient’s CRF. Each experience will be graded on a four-point scale (see **Appendix D**; mild, moderate, severe, life-threatening) as to severity. The date of onset as well as the duration of the experience will be recorded. In addition, the method used to treat the adverse experience and the outcome of the adverse experience will also be noted. The investigator will attempt to assess the relationship of the experience (unrelated, remote, possible, probable, related) to the test drug(s) (see **Appendix E**; Clinical Adverse Experiences: Determining Relationship to Test Drug).

13.1.3 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.4 Reporting of Pregnancy

We acknowledge that these are not serious unless a serious outcome is seen (e.g., miscarriage, congenital anomaly)

13.2 Definition of SAE

An SAE is any untoward medical occurrence that results in death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether or not expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:

http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized, and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Data and Safety Monitoring Plan (DSMP)

This is essentially a phase Ib trial with relatively slow accrual (1 patient every 4 months for each cohort). As a result, each patient's outcome will be reviewed upon completion of the procedure. The accrual will halt if the number of patients who have an unacceptable event (one that indicates the procedure is not safe) passes the stated threshold in the statistics section. All adverse events will be summarized and reported to the Weill Cornell Medicine DSMB every six months.

The Weill Cornell Medical College Data Safety Monitoring Board (WCMC DSMB) will be responsible for monitoring data quality and patient safety for this clinical study at WCMC. Subjects will receive two courses of IA chemotherapy with dosing that is consistent with its FDA approved clinical use. Study protocols follow routine clinical care. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, MRIs, etc. Subjects may choose to withdraw from the study at any time before or after drug administration. Preliminary analysis of the endpoints and adverse events will be submitted to the

WCMC DSMB semi-annually. Serious adverse events that fit the immediate reporting criteria will be reported to the WCMC DSMB and IRB immediately.

References:

- Abramson, D. H., Daniels, A. B., Marr, B. P., Francis, J. H., Brodie, S. E., Dunkel, I. J., & Gobin, Y. P. (2016). Intra-Arterial Chemotherapy (Ophthalmic Artery Chemosurgery) for Group D Retinoblastoma. *PLoS One*, 11(1), e0146582. doi:10.1371/journal.pone.0146582
- Abramson, D. H., Dunkel, I. J., Brodie, S. E., Kim, J. W., & Gobin, Y. P. (2008). A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. *Ophthalmology*, 115(8), 1398-1404, 1404 e1391. doi:10.1016/j.ophtha.2007.12.014
- Abramson, D. H., Dunkel, I. J., Brodie, S. E., Marr, B., & Gobin, Y. P. (2010). Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). *Ophthalmology*, 117(8), 1623-1629. doi:10.1016/j.ophtha.2009.12.030
- Abramson, D. H., Francis, J. H., & Gobin, Y. P. (2019). What's New in Intra-Arterial Chemotherapy for Retinoblastoma? *Int Ophthalmol Clin*, 59(2), 87-94. doi:10.1097/IIO.0000000000000266
- Abramson, D. H., Marr, B. P., Dunkel, I. J., Brodie, S., Zabor, E. C., Driscoll, S. J., & Gobin, Y. P. (2012). Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results. *Br J Ophthalmol*, 96(4), 499-502. doi:10.1136/bjophthalmol-2011-300498
- Akella, S. S., Francis, J. H., Knezevic, A., Ostrovnya, I., Gobin, Y. P., Friedman, D., . . . Abramson, D. H. (2018). Growth patterns of survivors of retinoblastoma treated with ophthalmic artery chemosurgery. *PLoS One*, 13(5), e0197052. doi:10.1371/journal.pone.0197052
- Bracco, S., Leonini, S., De Francesco, S., Cioni, S., Gennari, P., Vallone, I. M., . . . Cerase, A. (2013). Intra-arterial chemotherapy with melphalan for intraocular retinoblastoma. *Br J Ophthalmol*, 97(9), 1219-1221. doi:10.1136/bjophthalmol-2013-303267
- Burkhardt, J. K., Riina, H. A., Shin, B. J., Moliterno, J. A., Hofstetter, C. P., & Boockvar, J. A. (2011). Intra-arterial chemotherapy for malignant gliomas: a critical analysis. *Interv Neuroradiol*, 17(3), 286-295. doi:10.1177/159101991101700302
- Chantada, G., & Schaiquevich, P. (2016). Intra-arterial Chemotherapy for Retinoblastoma. *JAMA Ophthalmol*, 134(10), 1202-1203. doi:10.1001/jamaophthalmol.2016.2724
- Chen, Q., Zhang, B., Dong, Y., Mo, X., Zhang, L., Xia, J., . . . Zhang, S. (2019). Intra-arterial chemotherapy as primary or secondary treatment for infants diagnosed with advanced retinoblastoma before 3 months of age. *BMC Cancer*, 19(1), 693. doi:10.1186/s12885-019-5844-5
- Choi, S., Han, J. W., Kim, H., Kim, B. S., Kim, D. J., Lee, S. C., & Lyu, C. J. (2013). Combined chemotherapy and intra-arterial chemotherapy of retinoblastoma. *Korean J Pediatr*, 56(6), 254-259. doi:10.3345/kjp.2013.56.6.254
- Cloughesy, T. F., Gobin, Y. P., Black, K. L., Vinuela, F., Taft, F., Kadkhoda, B., & Kabbinavar, F. (1997). Intra-arterial carboplatin chemotherapy for brain tumors: a dose escalation study based on cerebral blood flow. *J Neurooncol*, 35(2), 121-131. doi:10.1023/a:1005856002264
- Dunkel, I. J., Shi, W., Salvaggio, K., Marr, B. P., Brodie, S. E., Gobin, Y. P., & Abramson, D. H. (2014). Risk factors for severe neutropenia following intra-arterial chemotherapy for intra-ocular retinoblastoma. *PLoS One*, 9(10), e108692. doi:10.1371/journal.pone.0108692
- Fitzpatrick, L. K., Aronson, L. J., & Cohen, K. J. (2002). Is there a requirement for adjuvant therapy for choroid plexus carcinoma that has been completely resected? *J Neurooncol*, 57(2), 123-126. doi:10.1023/a:1015773624733
- Francis, J. H., Gobin, Y. P., Dunkel, I. J., Marr, B. P., Brodie, S. E., Jonna, G., & Abramson, D. H. (2013). Carboplatin +/- topotecan ophthalmic artery chemosurgery for intraocular

- retinoblastoma. *PLoS One*, 8(8), e72441. doi:10.1371/journal.pone.0072441
- Gobin, Y. P., Cloughesy, T. F., Chow, K. L., Duckwiler, G. R., Sayre, J. W., Milanese, K., & Vinuela, F. (2001). Intraarterial chemotherapy for brain tumors by using a spatial dose fractionation algorithm and pulsatile delivery. *Radiology*, 218(3), 724-732. doi:10.1148/radiology.218.3.r01mr41724
- Gobin, Y. P., Dunkel, I. J., Marr, B. P., Brodie, S. E., & Abramson, D. H. (2011). Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. *Arch Ophthalmol*, 129(6), 732-737. doi:10.1001/archophthalmol.2011.5
- Gopal, P., Parker, J. R., Debski, R., & Parker, J. C., Jr. (2008). Choroid plexus carcinoma. *Arch Pathol Lab Med*, 132(8), 1350-1354. doi:10.1043/1543-2165(2008)132[1350:CPC]2.0.CO;2
- Greenberg, M. L. (1999). Chemotherapy of choroid plexus carcinoma. *Childs Nerv Syst*, 15(10), 571-577. doi:10.1007/s003810050545
- Haliasos, N., Brew, S., Robertson, F., Hayward, R., Thompson, D., & Chakraborty, A. (2013). Preoperative embolisation of choroid plexus tumours in children: part I-does the reduction of perioperative blood loss affect the safety of subsequent surgery? *Childs Nerv Syst*, 29(1), 65-70. doi:10.1007/s00381-012-1912-8
- Hoffman, C. E., Santillan, A., Rotman, L., Gobin, Y. P., & Souweidane, M. M. (2014). Complications of cerebral angiography in children younger than 3 years of age. *J Neurosurg Pediatr*, 13(4), 414-419. doi:10.3171/2013.12.PEDS13172
- Hudson, M. M., Ness, K. K., Gurney, J. G., Mulrooney, D. A., Chemaitilly, W., Krull, K. R., . . . Robison, L. L. (2013). Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA*, 309(22), 2371-2381. doi:10.1001/jama.2013.6296
- Jabbour, P., Chalouhi, N., Tjoumakaris, S., Gonzalez, L. F., Dumont, A. S., Chitale, R., . . . Shields, C. (2012). Pearls and pitfalls of intraarterial chemotherapy for retinoblastoma. *J Neurosurg Pediatr*, 10(3), 175-181. doi:10.3171/2012.5.PEDS1277
- Kemeny, N. E., Melendez, F. D., Capanu, M., Paty, P. B., Fong, Y., Schwartz, L. H., . . . D'Angelica, M. (2009). Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. *J Clin Oncol*, 27(21), 3465-3471. doi:10.1200/JCO.2008.20.1301
- Kikuchi, K., Hiwatashi, A., Togao, O., Yamashita, K., Kamei, R., Momosaka, D., . . . Honda, H. (2019). Intravoxel Incoherent Motion MR Imaging of Pediatric Intracranial Tumors: Correlation with Histology and Diagnostic Utility. *AJNR Am J Neuroradiol*, 40(5), 878-884. doi:10.3174/ajnr.A6052
- Lafay-Cousin, L., Mabbott, D. J., Halliday, W., Taylor, M. D., Tabori, U., Kamaly-Asl, I. D., . . . Bouffet, E. (2010). Use of ifosfamide, carboplatin, and etoposide chemotherapy in choroid plexus carcinoma. *J Neurosurg Pediatr*, 5(6), 615-621. doi:10.3171/2010.3.PEDS09354
- Lazzaro, M. A., Badruddin, A., Zaidat, O. O., Darkhabani, Z., Pandya, D. J., & Lynch, J. R. (2011). Endovascular embolization of head and neck tumors. *Front Neurol*, 2, 64. doi:10.3389/fneur.2011.00064
- Lian, F., Chen, W., Liu, Y., Shen, L., Fan, W., Cui, W., . . . Wang, Y. (2019). Intra-arterial chemotherapy combined with intravesical chemotherapy is effective in preventing recurrence in non-muscle invasive bladder cancer. *J Cancer Res Clin Oncol*, 145(6), 1625-1633. doi:10.1007/s00432-019-02900-8
- Lin, Q., Li, Z., Zhang, L., Zhang, S., Xu, G., Guo, L., & An, D. (2002). Effects on micro-vessel density after pre-operative intra-arterial infusion chemotherapy in colorectal cancer. *Chinese journal of oncology*, 24(1), 84-86.
- Liu, Z., Ye, Y., Li, X., Guo, S., Jiang, L., Dong, P., . . . Liu, Z. (2018). The effects of intra-arterial chemotherapy on bladder preservation in patients with T1 stage bladder cancer. *World J Urol*, 36(8), 1191-1200. doi:10.1007/s00345-018-2199-5

- Manjandavida, F., Stathopoulos, C., Zhang, J., Honavar, S., & Shields, C. (2019). Intra-arterial chemotherapy in retinoblastoma – A paradigm change. *Indian Journal of Ophthalmology*, 67(6), 740-754. doi:10.4103/ijo.IJO_866_19
- Noguchi, T., Yoshiura, T., Hiwatashi, A., Togao, O., Yamashita, K., Nagao, E., . . . Honda, H. (2008). Perfusion imaging of brain tumors using arterial spin-labeling: correlation with histopathologic vascular density. *AJNR Am J Neuroradiol*, 29(4), 688-693. doi:10.3174/ajnr.A0903
- Ostrom, Q. T., Gittleman, H., Xu, J., Kromer, C., Wolinsky, Y., Kruchko, C., & Barnholtz-Sloan, J. S. (2016). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. *Neuro Oncol*, 18(suppl_5), v1-v75. doi:10.1093/neuonc/now207
- Packer, R. J., Perilongo, G., Johnson, D., Sutton, L. N., Vezina, G., Zimmerman, R. A., . . . Schut, L. (1992). Choroid plexus carcinoma of childhood. *Cancer*, 69(2), 580-585. doi:10.1002/1097-0142(19920115)69:2<580::aid-cnrcr2820690250>3.0.co;2-o
- Palioura, S., Gobin, Y. P., Brodie, S. E., Marr, B. P., Dunkel, I. J., & Abramson, D. H. (2012). Ophthalmic artery chemosurgery for the management of retinoblastoma in eyes with extensive (>50%) retinal detachment. *Pediatr Blood Cancer*, 59(5), 859-864. doi:10.1002/pbc.24170
- Passariello, A., Tufano, M., Spennato, P., Quaglietta, L., Verrico, A., Migliorati, R., & Cinalli, G. (2015). The role of chemotherapy and surgical removal in the treatment of Choroid Plexus carcinomas and atypical papillomas. *Childs Nerv Syst*, 31(7), 1079-1088. doi:10.1007/s00381-015-2697-3
- Pencalet, P., Sainte-Rose, C., Lellouch-Tubiana, A., Kalifa, C., Brunelle, F., Sgouros, S., . . . Renier, D. (1998). Papillomas and carcinomas of the choroid plexus in children. *J Neurosurg*, 88(3), 521-528. doi:10.3171/jns.1998.88.3.0521
- Peterson, E. C., Elhamady, M. S., Quintero-Wolfe, S., Murray, T. G., & Aziz-Sultan, M. A. (2011). Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: initial experience with 17 tumors. *J Neurosurg*, 114(6), 1603-1608. doi:10.3171/2011.1.JNS10466
- Pierga, J. Y., Kalifa, C., Terrier-Lacombe, M. J., Habrand, J. L., & Lemerle, J. (1993). Carcinoma of the choroid plexus: a pediatric experience. *Med Pediatr Oncol*, 21(7), 480-487. doi:10.1002/mpo.2950210705
- Schneider, C., Kamaly-Asl, I., Ramaswamy, V., Lafay-Cousin, L., Kulkarni, A. V., Rutka, J. T., . . . Taylor, M. D. (2015). Neoadjuvant chemotherapy reduces blood loss during the resection of pediatric choroid plexus carcinomas. *J Neurosurg Pediatr*, 16(2), 126-133. doi:10.3171/2014.12.PEDS14372
- Shapiro, W. R., & Green, S. B. (1987). Reevaluating the efficacy of intra-arterial BCNU. *J Neurosurg*, 66(2), 313-315. doi:10.3171/jns.1987.66.2.0313
- Shields, C. L., Bianciotto, C. G., Jabbour, P., Griffin, G. C., Ramasubramanian, A., Rosenwasser, R., & Shields, J. A. (2011). Intra-arterial chemotherapy for retinoblastoma: report No. 2, treatment complications. *Arch Ophthalmol*, 129(11), 1407-1415. doi:10.1001/archophthalmol.2011.151
- Shields, C. L., Kaliki, S., Shah, S. U., Bianciotto, C. G., Liu, D., Jabbour, P., . . . Shields, J. A. (2012). Minimal exposure (one or two cycles) of intra-arterial chemotherapy in the management of retinoblastoma. *Ophthalmology*, 119(1), 188-192. doi:10.1016/j.ophtha.2011.06.036
- Shields, C. L., Manjandavida, F. P., Lally, S. E., Pieretti, G., Arepalli, S. A., Caywood, E. H., . . . Shields, J. A. (2014). Intra-arterial chemotherapy for retinoblastoma in 70 eyes: outcomes based on the international classification of retinoblastoma. *Ophthalmology*, 121(7), 1453-1460. doi:10.1016/j.ophtha.2014.01.026
- Shields, C. L., & Shields, J. A. (2010). Intra-arterial chemotherapy for retinoblastoma: the

- beginning of a long journey. *Clin Exp Ophthalmol*, 38(6), 638-643. doi:10.1111/j.1442-9071.2010.02297.x
- Slater, L. A., Hoffman, C., Drake, J., & Krings, T. (2016). Pre-operative embolization of a choroid plexus carcinoma: review of the vascular anatomy. *Childs Nerv Syst*, 32(3), 541-545. doi:10.1007/s00381-015-2851-y
- Souweidane, M. M., Johnson, J. H., Jr., & Lis, E. (1999). Volumetric reduction of a choroid plexus carcinoma using preoperative chemotherapy. *J Neurooncol*, 43(2), 167-171. doi:10.1023/a:1006229732653
- St Clair, S. K., Humphreys, R. P., Pillay, P. K., Hoffman, H. J., Blaser, S. I., & Becker, L. E. (1991). Current management of choroid plexus carcinoma in children. *Pediatr Neurosurg*, 17(5), 225-233. doi:10.1159/000120602
- Sun, M. Z., Oh, M. C., Ivan, M. E., Kaur, G., Safaee, M., Kim, J. M., . . . Parsa, A. T. (2014). Current management of choroid plexus carcinomas. *Neurosurg Rev*, 37(2), 179-192; discussion 192. doi:10.1007/s10143-013-0499-1
- Tabori, U., Shlien, A., Baskin, B., Levitt, S., Ray, P., Alon, N., . . . Malkin, D. (2010). TP53 alterations determine clinical subgroups and survival of patients with choroid plexus tumors. *J Clin Oncol*, 28(12), 1995-2001. doi:10.1200/JCO.2009.26.8169
- Thampi, S., Hettis, S. W., Cooke, D. L., Stewart, P. J., Robbins, E., Banerjee, A., . . . Matthay, K. (2013). Superselective intra-arterial melphalan therapy for newly diagnosed and refractory retinoblastoma: results from a single institution. *Clin Ophthalmol*, 7, 981-989. doi:10.2147/OPTH.S43398
- Vajzovic, L. M., Murray, T. G., Aziz-Sultan, M. A., Scheffler, A. C., Wolfe, S. Q., Hess, D., . . . Dubovy, S. R. (2011). Supraselective intra-arterial chemotherapy: evaluation of treatment-related complications in advanced retinoblastoma. *Clin Ophthalmol*, 5, 171-176. doi:10.2147/OPTH.S12665
- Venturi, C., Bracco, S., Cerase, A., Cioni, S., Galluzzi, P., Gennari, P., . . . Hadjistilianou, T. (2013). Superselective ophthalmic artery infusion of melphalan for intraocular retinoblastoma: preliminary results from 140 treatments. *Acta Ophthalmol*, 91(4), 335-342. doi:10.1111/j.1755-3768.2011.02296.x
- Wang, H. H., Luo, C. B., Guo, W. Y., Wu, H. M., Lirng, J. F., Wong, T. T., . . . Chang, F. C. (2013). Preoperative embolization of hypervascular pediatric brain tumors: evaluation of technical safety and outcome. *Childs Nerv Syst*, 29(11), 2043-2049. doi:10.1007/s00381-013-2128-2
- Wrede, B., Hasselblatt, M., Peters, O., Thall, P. F., Kutluk, T., Moghrabi, A., . . . Wolff, J. E. A. (2009). Atypical choroid plexus papilloma: clinical experience in the CPT-SIOP-2000 study. *J Neurooncol*, 95(3), 383-392. doi:10.1007/s11060-009-9936-y
- Wrede, B., Liu, P., & Wolff, J. E. (2007). Chemotherapy improves the survival of patients with choroid plexus carcinoma: a meta-analysis of individual cases with choroid plexus tumors. *J Neurooncol*, 85(3), 345-351. doi:10.1007/s11060-007-9428-x
- Wyse, E., Handa, J. T., Friedman, A. D., & Pearl, M. S. (2016). A review of the literature for intra-arterial chemotherapy used to treat retinoblastoma. *Pediatr Radiol*, 46(9), 1223-1233. doi:10.1007/s00247-016-3554-6
- Zahringer, M., Guntinas-Lichius, O., Gossmann, A., Wustrow, J., Kruger, K., & Lackner, K. (2005). Percutaneous embolization for cervicofacial neoplasms and hemorrhages. *ORL J Otorhinolaryngol Relat Spec*, 67(6), 348-360. doi:10.1159/000090047

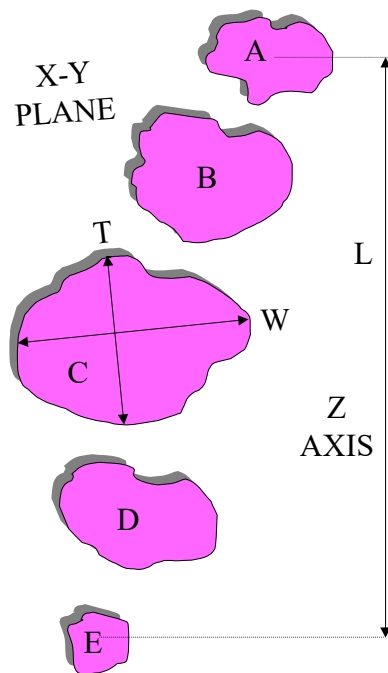
Appendix I**i) General Methodology for Determining Tumor Volume**

3D (volume) tumor dimensions are determined by measurement of the longest tumor dimension and its perpendicular and the length (perpendicular to the plane of the axial measurement) for each target lesion. Regarding MRI imaging, the post-Gad 3D T1 will always be chosen for measurement. Response determination will be based on a comparison of a 3D (volume; $W \times T \times L$ — see below) between the baseline assessment and the visit date designated during the treatment phase. Reports for the visit exams should reiterate the measurements obtained at baseline for each target lesion. Newly occurring lesions should also be enumerated in these reports.

1. The longest diameter (LD) will only be measured on the axial plane. This longest measurement of the tumor is referred to as the width (W).
2. The perpendicular measurements should be determined - transverse (T) measurement, perpendicular to the width in the selected plane.
3. The length (L) is then measured as the perpendicular to the plane defined by measurements in 1 and 2.
4. The cystic or necrotic components of a tumor are typically not considered in tumor measurements. Therefore, only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis composes the majority of the lesion, the lesion may not be “measurable”.

Options:

- if the cyst/necrosis is eccentric, the W and T (and L) of the solid portion should be measured, the cyst/necrosis excluded from measurement.
- if the cyst/necrosis is central but represents a small portion of the tumor (< 25%), disregard and measure the whole lesion.
- if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured.



**COG GUIDELINE: TUMOR SIZE
MEASUREMENT BASED ON
CROSS-SECTIONAL IMAGING**

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

b) Selection of Target Lesions

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a “target” for measurement/follow up to assess for tumor progression/response.
2. In case of a bifocal lesion both lesions should be selected as “target” lesions.
3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

c) Volumetric Response Criteria for Target Lesions

1. Response criteria are assessed in 3 (volume) (or 2 (area) if 3 not possible) dimensions – the product of W x T x (L).
2. To assess response/progression, the ratio is calculated (x 100 = %):

$$\frac{W \times T \times (L) \text{ (current scan)}}{W \times T \times (L) \text{ (reference scan)}}$$
3. Development of new disease or progression in any established lesions is considered progressive disease (PD), regardless of response in other lesions – e.g., even when multiple lesions show opposite responses, the progressive disease takes precedence.

Response criteria for target lesions are:

- **Complete Response (CR):** Complete disappearance of visible disease on imaging allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.
- **Continued Complete Response (CCR):** Continuing absence of radiographically identifiable disease allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.
- **Partial Response (PR):** > 0.5 cm dimension residual in the suprasellar area or > 1 cm residual in case of pineal involvement after completion of chemotherapy, but $\geq 65\%$ decrease in the sum of the products of the three perpendicular diameters (volume) of all target lesions (up to 5), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the three perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started) and residual disease after chemotherapy of > 1.5 cm maximal diameter.
- **Progressive Disease (PD):** 40% or more increase in the product of perpendicular diameters (volume) of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions. If a growing lesion is later found to represent growing teratoma or fibrosis, the patient will be considered to have a CR/PR.

In the circumstance that 3-D measurement cannot be determined, maximal diameter in a 2-D measurement (area) would be used to evaluate response: TxW (product of the longest diameter and its longest perpendicular diameter).

- **Complete Response (CR):** Complete disappearance of visible disease on imaging allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.
- **Partial Response (PR):** > 0.5 cm maximal dimension residual in the suprasellar area or > 1 cm residual in case of pineal involvement after completion of chemotherapy, but more than $\geq 50\%$ decrease in 2-D (area) measurement.
- **Stable Disease (SD):** Decrease in $< 50\%$ of all target lesions and residual disease after chemotherapy of > 1.5 cm maximal diameter.
- **Progressive Disease (PD):** Defined as $\geq 25\%$ increase 2-D (area) of target lesion(s) or development of any new lesions irrespective of the response of the initial lesions. If a growing lesion is later found to represent growing teratoma or fibrosis, the patient will be considered to have a CR/PR.