THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

Phase II Randomized Trial of Radiotherapy Followed by intravitreal Aflibercept injection for patients with ocular melanoma

Principal Investigator:	Wenyin Shi, MD., PhD. Department of Radiation Oncology 111 S 11 ST, Suite G301 Philadelphia, PA 19107 Phone: (215) 955-6702 Fax: (215) 955-0412
Co-Investigator(s):	Thomas Jefferson University Lydia Komarnicky-Kocher Department of Radiation Oncology 111 S 11 ST, Suite G301 Philadelphia, PA 19107 Phone: (215) 955-6702 Fax: (215) 955-0412 Maria Werner-Wasik, MD Department of Radiation Oncology 111 S 11 ST, Suite G301 Philadelphia, PA 19107 Phone: (215) 955-6702 Fax: (215) 955-0412 Voichita Bar Ad, MD Department of Radiation Oncology 111 S 11 ST, Suite G301 Philadelphia, PA 19107 Phone: (215) 955-6702 Fax: (215) 955-0412 **Wills Eye Hospital** Carol Shields, MD Wills Eye Hospital 840 Walnut Street, Suite 1440 Philadelphia, PA 19107 Phone: (877) 289-4557 Fax: (215) 928-1140 Sara Lally, MD Wills Eye Hospital 840 Walnut Street, Suite 1440 Philadelphia, PA 19107

	Phone: (877) 289-4557 Fax: (215) 928-1140
Statistician:	Inna Chervoneva, PhD
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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Wenyin Shi, MD

Title: Professor

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IAI	Intravitreal Aflibercept Injection
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control

SAE	Serious Adverse Event/Serious Adverse Experience
SBRT	Stereotactic Body Radiotherapy
SKCC	Sidney Kimmel Cancer Center
SOP	Standard Operating Procedure
SRT	Stereotactic Radiotherapy
TJU	Thomas Jefferson University
UAP	Unanticipated Problem

Study Summary

Title: Phase II Randomized Trial of Radiotherapy Followed by intravitreal Aflibercept injection for patients with ocular Melanoma

Précis: Patients with localized ocular melanoma will be eligible to participate in this 2-arm randomized study. Patients in arm A will receive Radiation treatment (either Plaque brachytherapy or SRT to a total dose of 50Gy in 5 fractions) followed by an injection of intravitreal Aflibercept injection (IAI) at 4 months after completion of radiation treatment and repeat injections every 2 months afterwards for a total of 2 years (11 injections). Patients in arm B will receive the same radiation treatment followed by an injection of intravitreal Aflibercept injection (IAI) at 4 months after completion of radiation treatment and repeat injections every 4 months for a total of 2 years (6 injections). Primary endpoint will be safety. Secondary endpoints will include 2-year radiation maculopathy rate, radiation papilopathy rate, radiation glaucoma rate, local control, progression-free survival, and vision preservation rate.

Objectives:

Primary:

Safety of therapy as defined by percent of patients with CTCAE v5.0 grade 3 or higher toxicity

Secondary:

2-year radiation maculopathy rate

2-year radiation papilopathy rate

2-year radiation glaucoma rate

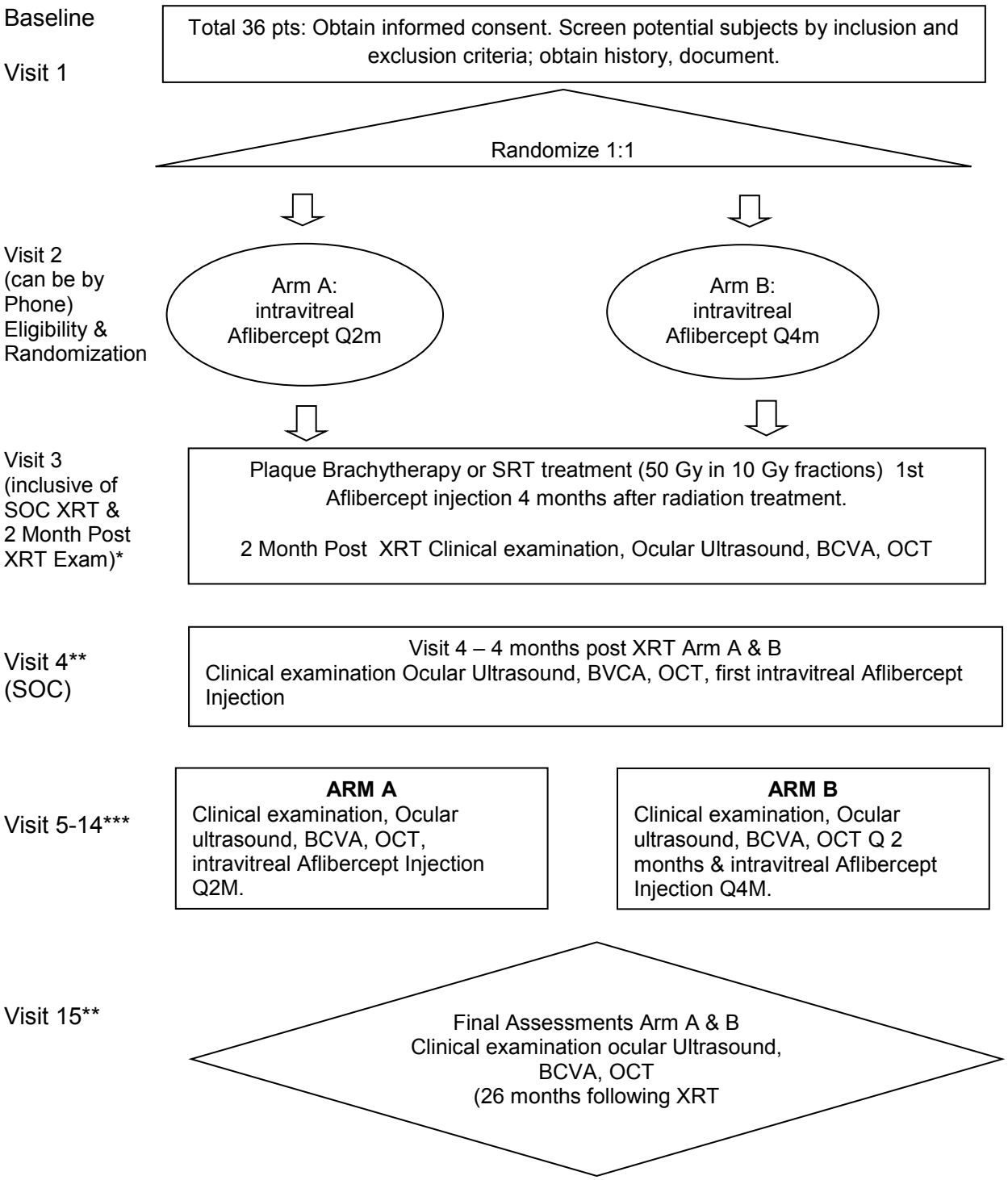
2-year local control

2-year progression-free survival

2-year vision preservation rate

Population:	36 patients with localized uveal melanoma of one eye, male or female, age ≥18, who are otherwise fit to undergo radiation therapy and intravitreal injections
Phase:	II randomized
Number of Sites:	1 Jefferson Hospital for Neuroscience
Description of Intervention:	Patients will be randomly assigned to one of two different dosing intervals of injections of intravitreal Aflibercept, a novel anti-VEGF drug, after finishing radiation treatment of the eye. The dose of IAI administered will be identical in both arms at 2 mg per injection. The first dose in both arms will be administered 4 months after the completion of radiation treatment. Patients in arm A will then receive one 2mg injection every 2 months for a total 2 years duration (11 injections total). Patients in arm B will receive one 2 mg injection every 4 months for 2 years duration (6 total injections).
Study Duration:	30 months for patient enrollment window. Study will end 6 months after last enrolled patient completed the final study visit and study analysis (40 months after finishing radiation treatment)
Participant Participation Duration:	2.5 years
Estimated Time to Complete Enrollment:	30 months

Schematic of Study Design:



* Plaque brachytherapy, or SRT (total of 5 treatments, every other day weekdays only, acceptable variation: every day treatment). All treatment should finish within 10 days (acceptable range: 14 days)

** Acceptable range for each visit: ± 2 weeks
***stratification: Fractionated SRT vs Radioactive plaque Brachytherapy

1 Introduction

1.1 Background Information

Uveal tract melanoma is the most common adult primary intraocular malignancy and is the only known potentially lethal intraocular tumor(1). Most patients who develop uveal melanoma fall within the age range of 50-80 years, with median age at diagnosis of 58 years. The majority of uveal melanomas arise in the choroidal and ciliary body, and are together designated as posterior uveal melanomas. Iris melanomas are less common, representing approximately 2-4% of all uveal tract melanomas, and tend to have a more benign natural history compared to posterior uveal melanomas. Iris melanomas tend to occur more commonly in young patients (age < 20 years), and may represent approximately 20% of all uveal melanomas in that age group(2). Unlike cutaneous melanoma, exposure to solar UV radiation has not been shown to be a reliable risk factor for development of uveal melanoma(3). However, other factors that have been linked to increased incidence of uveal melanoma include history of atypical cutaneous nevi, cutaneous freckles, and iris nevi (4).

Uveal melanomas are often asymptomatic on presentation, and are frequently diagnosed on routine ophthalmologic evaluation. However, depending on location, patients may demonstrate local symptoms such as visual distortion, blurry vision, diplopia, ocular pain, or conjunctival injection (5). Typically, choroidal melanomas present as a mushroom-shaped sub-retinal mass and tumor growth can lead to retinal detachment and subsequent blindness. Melanomas arising in the ciliary bodies can lead to lens displacement causing visual distortion or elevation in ocular pressure as outflow maybe obstructed. Melanomas of the iris are usually visible as a pigmented lesion, and may also present with pupillary distortion, hyphema, or outflow obstruction leading to secondary glaucoma. Regardless of location, the vast majority of uveal melanomas are diagnosed clinically, without need for biopsy, with very high (>99%) accuracy (6).

While local effects of tumor place the patient at risk for visual deficits or vision loss, the most common cause of death in these patients comes from metastatic dissemination of disease. Fortunately, at time of initial diagnosis, a minority (<4%) of patients have detectable metastatic disease burden (7). Uveal melanoma demonstrates a hematogenous route of spread, with the liver representing the most frequent site of initial metastasis (93%), followed by lung (24%), and bone (16%) (8). Spread to regional lymph nodes is uncommon given the lack of lymphatic supply from the uveal tract, however, may occur in cases where the tumor invades into the conjunctiva and metastasizes through those associated draining lymphatics to regional lymph nodes(9).

Incidence of metastatic development at 10 years from initial diagnosis is around 33%, 25%, and 7% for melanomas of the ciliary body, choroid, and iris respectively (10).

Overall mortality from ocular melanoma patients is approximately 19% at 5 years and 35% at 10 years from diagnosis (11). After development of metastatic disease, however, prognosis becomes extremely poor, with 80% of patients dying within 1 year, and 90% dying within 2 years (12).

The standard treatment for all uveal melanoma patients was historically enucleation. However, radiation treatment has now replaced enucleation as standard of care in patients with early stage disease. The main advantage of radiation over surgical treatment is eye preservation, and therefore potential for vision sparing. A landmark study investigating the efficacy of radiation therapy for definitive treatment of non-metastatic uveal melanoma was carried out by the Collaborative Ocular Melanoma Study group (COMS). In that trial, a total of 1317 patients were enrolled from 1989 – 2003, and underwent randomization between surgical enucleation versus radiation therapy with plaque brachytherapy. Since the study was completed, the 12-year follow-up analysis has been published which has demonstrated no difference in overall survival, progression-free survival, or death with melanoma metastasis in the radiation group as compared to the enucleation group. The COMS study had led to the adoption of I-125 based plaque brachytherapy as the most commonly used form of radiation treatment for this disease (11, 12).

In addition to brachytherapy, external beam radiation is a current standard of care for radiation treatment of uveal melanomas. One limitation of brachytherapy remains large tumor size. As tumor size increases, the ability of brachytherapy to adequately cover the entire tumor volume decreases. Typical upper bounds for tumor basal diameter and tumor thickness are around 22mm and 12 mm respectively for I-125 and 20mm and 6mm respectively for Ru-106 when considering plaque brachytherapy(13). In addition to large tumor size, proximity of tumor to the optic disc is often a disqualification criteria for plaque brachytherapy, as the tumor would receive inadequate dose coverage. While notched plaques can allow treatment of some tumors close to the optic disc, tumors abutting, or within a few millimeters of the optic disc remain controversial and remains cautionary per the American Brachytherapy Society guidelines (13). For those patients who are poor candidates for plaque brachytherapy based on the above or any other factors, external beam radiation generally remains a safe treatment option.

Early studies in external beam radiation therapy for these tumors was generally performed with proton-beam therapy. Proton therapy was pioneered by Gragoudas et al in the early 1980’s. They described their initial experience treating 76 uveal melanoma patients, who were otherwise not favorable brachytherapy candidates either due to proximity of tumor to the fovea or due to tumor size. Treatment planning included suturing of small tantalum markers to the sclera for tumor localization, and instructing

patients to maintain a fixed gaze to an LED light attached to the collimator for eye immobilization. Dose delivered was 70Gy fractionated over 5 consecutive days. Their results demonstrated excellent overall survival for patients with small tumors at 5-years comparable to plaque brachytherapy, but importantly, also demonstrated 5 year survival of over 55% for patients with large tumors who would otherwise not be suitable for vision-sparing treatment, while maintaining acceptable toxicity profiles (14). This study was followed by investigation of dose de-escalation which compared efficacy of 50 Gy delivered in 5 fractions to the previously used 70 Gy in 5 fractions in a group of 188 patients with tumor close to (within 4 disc diameters) either the optic disc of macula. No difference was seen in local control or in development of metastatic disease between the two differing doses. However, patients treated with 50 Gy experienced significantly less visual field loss compared to those receiving 70 Gy, suggesting 50 Gy to be an effective and safe dose to use (15).

Photon-based SRS treatment has also been reported in published experiences demonstrating comparable rates of local control in patients who are poor candidates from plaque brachytherapy due to unfavorable tumor characteristics. Sikuade et al reported their experience treating 106 pts with proton beam therapy (PBT) and 85 patients treated with photon-based SRS using GammaKnife (GK) (16). Patients treated with EBRT had tumors that were either too large for brachytherapy (>16mm basal diameter or >6.5mm thick) or too close to the optic disc (<2.5 disc diameters). Patients who received protons were treated with similar set up to that described by Gragoudas et al, and were treated to a total dose of 53.1 CGE in 4 daily fractions. Patients treated with GK were treated to a total dose of 35 Gy in a single fraction. Eye immobilization in GK patients was achieved through retrobulbar anesthesia to temporarily paralyze the extraocular muscles. With median follow up time of 39 months, rates of radiation retinopathy were similar, and eye retention rates were high in both arms (95-98%). Post treatment visual acuity was slightly lower in the SRS arm compared to PBT arm (33% vs 55% with visual acuity >6/60), although this was confounded by a statistically higher number of patients with poor initial vision in the SRS arm as compared to the PBT arm. Another retrospective series described results of linac-based SRS treatment for posterior uveal melanomas treated to a total dose of 37-52Gy (Median dose 49 Gy). Of the 96 patients analyzed, 3 year and 5 year local control was excellent at 95% and 85% respectively (17).

Although radiation treatment is highly effective in achieving local tumor control, radiation therapy may be associated with concerning treatment-related morbidity. The most common severe adverse effects of radiation therapy include retinopathy, papillopathy, cataract formation, glaucoma, and potentially, loss of serviceable vision (2, 18). The majority of these complications occur as late effects of treatment. The average time to onset of radiation papillopathy is approximately 18 months post-radiation treatment. The median time to development of optical coherence tomography (OCT)- evident radiation induced maculopathy is approximately 12 months, although may be seen as early as 4

months after completion of plaque-based brachytherapy (18). The development of OCT-evident maculopathy is particularly important as this was found to significantly predict for subsequent loss of serviceable vision (18). Given this finding, radiation maculopathy and retinopathy are important toxicities to evaluate for and potentially mitigate.

Inflammatory mediators and angiogenic factors are suspected to play a role in the pathogenesis of radiation maculopathy. In patients treated with plaques, it is found that prophylactic anti-VEGF agents can prevent and minimize radiation maculopathy (18, 19). Previous experience with injection of intravitreal bevacizumab has been shown to reduce the 2-year cumulative incidence of OCT-evident maculopathy from 40% down to 26% in those patients who underwent radioactive plaque brachytherapy alone versus plaque brachytherapy followed by 2 years of q4 month bevacizumab injections respectively (18). In this same study, the addition of intravitreal bevacizumab reduced the rate of clinically evident radiation retinopathy from 31% down to 16%, and reduced moderate vision loss from 57% down to 33% (18).

In this study, we propose treatment of uveal melanoma patients with radiation treatment with the addition IAI with goal to reduce radiation-related vision-threatening toxicity. Aflibercept is a recombinant fusion protein composed of extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. This drug is formulated as an iso-osmotic solution for intravitreal administration. We hypothesize intravitreal injection of aflibercept after radiation treatment for uveal melanoma will significantly reduce radiation induced ocular toxicity when delivered over a time period in which clinically meaningful toxicity including radiation papillopathy and retinopathy are known to develop.

1.2 Rationale for the Proposed Study

The patient population being selected for this study are those patients with non-metastatic uveal melanoma. External beam radiation, with stereotactic technique, or brachytherapy can be used for eye preservation alternative to encleation. Radiation therapy to these tumors has well described risk of toxicity including radiation induced papillopathy and maculopathy, which may lead to deterioration in vision. VEGF and neovascularization is thought to play an important role in the development of these vision threatening toxicities. Therefore, we hypothesize that the addition of intravitreal Aflibercept, after completion of radiation therapy, will reduce the incidence of these adverse reactions.

IAI is currently FDA approved for multiple ocular pathology indication including wet macular degeneration, diabetic maculopathy, and macular edema following retinal vein occlusion. It also has been reported to successfully treat post-radiation retinopathy (20-22). The route of administration of this recombinant fusion protein is via intravitreal injection. In this manner, the systemic dose of IAI is negligible while at therapeutic levels within the globe. The dosage per injection for this study was chosen to match that of the

dosage of intravitreal Alfibercept in it's currently FDA approved indications of 2mg/injection. The dosing frequency of IAI in currently approved indications range from q1-2 months. One arm in the proposed trial will therefore use the injection frequency of q2 months. For the other arm, we will investigate a q4 month dosing regimen, to better align with current standard follow-up time frames for patients who undergo plaque brachytherapy without further therapy.

1.3 Correlative Studies

No planned correlative studies.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

System Organ Class	Very Common	Common	Uncommon	Rare
Immune System Disorders			Hypersensitivity***	
Eye Disorders	Conjunctival hemorrhage, Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid edema, Injection site hemorrhage, Punctate keratitis,	Endophthalmitis**, Retinal detachment, Retinal tear, Uveitis, Iritis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Anterior chamber flare, Corneal edema	Cataract traumatic, Vitritis, Hypopyon

		Conjunctival hyperemia, Ocular hyperemia		

*Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
**Culture positive and culture negative endophthalmitis
***During the post-marketing period, reports of hypersensitivity included rash, pruritis, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors.

1.4.2 **Benefits**

We are investigating the hypothesis that the addition of IAI to radiation will reduce the incidence of several different potential side effects that are known to occur after radiation therapy. These side effects may directly or indirectly lead to deterioration in vision. Therefore, possible benefit for enrollment in this study is to receive IAI with goal to improve chance of maintaining functional visual acuity and minimizing other radiation related side effects.

2 Study Objectives

2.1 Objectives

2.1.1 **Primary**

To assess the percentage of patients able to successfully complete their prescribed treatment of radiation and/or IAI with an acceptable level of toxicity.

2.1.2 **Secondary**

To assess for reduction in the incidence of 2 year rates of radiation maculopathy, radiation papillopathy, functional vision preservation, radiation glaucoma, and to assess 2 year local control and progression-free survival.

An interim analysis is planned when all patients have completed 1 year of follow-up.

2.2 Endpoints/Outcome Measures

2.2.1 **Primary**

Percent of patients who experience Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade ≥3 toxicity related to SRT and/or intravitreal Aflibercept.

2.2.2 **Secondary**

- 2-year rates of radiation maculopathy, defined as ophthalmoscopic detection of macular edema, retinal hemorrhage, retinal exudation, nerve fiber layer infarction, perivascular sheathing, and retinal or optic disc neovascularization
- 2-year rates of radiation papillopathy, defined as ophthalmoscopic detection of peripapillary encircling nerve fiber layer infarction, disc edema, or disc pallor
- 2-year rates of functional vision preservation defined as less than moderate vision loss (in pts with functional vision prior to study treatment). Moderate vision loss is defined as loss of 15 ETDRS letters or more of best-corrected visual acuity compared with presentation
- 2-year rates of radiation glaucoma.
- 2-year local control rate
- 2-year progression-free survival rate.

3 Study Design

This is a single center phase II, 2-arm, randomized clinical trial, investigating the addition of IAI in patients with non-metastatic uveal melanoma treated with radiation therapy (plaque brachytherapy or SRT). The patients will be treated on an outpatient basis. The first intravitreal injection of the study drug will occur 4 months after the completion of radiation treatment, and the remainder of the injections will be given over the following 2 years, at an interval specified by the randomization arm. Research subjects will be followed up every 2 months after completion of radiation, and will undergo an updated history and physical exam, including detailed eye exam and OCT exam which will be performed at Wills Eye Hospital.

Wills Eye Hospital will be considered a research location under the single site (Thomas Jefferson University) for this trial. Both TJU IRB and WEH IRB will have oversight of this trial.

3.1 Number of Participants

36 pts, 18 in each arm

3.2 Duration of Therapy

FSRT will be given over 5 treatments every other day, weekday only (Acceptable range: all 5 treatment delivered no longer than 14 days).The plaque brachytherapy will be delivered over ~100 hr (acute time will base on the calculation). The first dose of IAI will be administered 4 months after the completion of SRT or plaque removal (acceptable range: ± 2 weeks) and then every 2 or 4 months from the first IAI dose (acceptable range ± 2 weeks) for a total of 2 years, depending on the randomization arm. Therefore, total duration of therapy will be 2 years and 2 months.

3.3 Duration of Follow Up

On study follow-up will last for 2 months after last treatment with study drug.

3.4 Treatment Assignment Procedures

3.4.1 Randomization Procedures (if applicable)

The type of radiation (plaque brachytherapy or SRT) is determined by treating physician. Patients will be randomized in a 1:1 fashion between the two arms of this study. Patients will be randomized upon enrollment (Baseline/Enrollment Visit) using RedCap which was developed by the study statistician.

3.4.2 Masking Procedures (if applicable)

No masking will be performed for this study.

3.5 Study Timeline

3.5.1 Primary Completion

Primary completion will be reached once the final patient completes their last scheduled injection of intravitreal Aflibercept.

3.5.2 Study Completion

Study completion will be reached once the final patient completes their 2 month post-completion-of- IAI follow-up visit.

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Provide signed and dated informed consent form or have a Legally Authorized Representative (LAR) who can give consent
2. Willing to comply with all study procedures and be available for the duration of the study
3. Male or female, aged ≥ 18 years

4. Must be a candidate for radiation therapy
5. KPS≥60
6. Diagnosed with uveal melanoma either clinically or pathologically on biopsy.
7. Uveal melanoma of one eye only
8. Localized uveal melanoma, with no evidence of metastasis
9. Women of childbearing potential must have a negative urine or serum pregnancy test within 14 days prior to enrollment

4.1.2 **Exclusion Criteria**

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Tumor thickness more than 14 mm as measured by ultrasound
2. Active collagen vascular disease
3. Any contraindication to intravitreal injections including: elevated intraocular pressure, ocular or periocular infection, active intraocular inflammation, or other determined by treating physician.
4. Known allergic reactions to components of intravitreal Aflibercept
5. Patients with known hypercoagulable syndromes.
6. Prior radiation to the eye or brain
7. Life expectancy less than 6 months
8. Blind in both eyes
9. Deaf in both ears
10. Patients are on or within 1 month of systemic anti-VEGF treatment
11. Patients for whom enucleation is standard of care
12. Pregnancy or active breastfeeding. Sexually active men* or women of childbearing potential** who are unwilling to practice adequate contraception

prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose. Adequate contraceptive measures include stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly.

*Contraception is not required for men with documented vasectomy.

**Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

4.2 Gender/Minority/Pediatric Inclusion for Research

Pediatric (age <18 years) patients are excluded from this study. Both male and female patients are eligible for this study as are minority patients. The male to female ratio in this disease is about 1.3:1.The accrual will be monitored by the MDG quarterly and if enrollment does not reflect the known incidence, a plan to increase recruitment of women will be made.

4.3 Strategies for Recruitment and Retention

Patients will not receive direct financial compensation by enrollment into this study, however, the investigational drug will be supplied free-of-cost. Patients will be enrolled at Radiation Oncology at Thomas Jefferson University Hospital (TJUH). Patients will be retained in close follow-up at a frequency close to the standard of care for patients receiving plaque brachytherapy for treatment of their tumor, therefore, no significant additional burden of follow-up is anticipated through enrollment onto this study.

4.4 Participant Enrollment

All potential patients will be consented at Radiation Oncology at TJUH. Eligibility will be confirmed by the Principal Investigator or the listed Co-Investigators from TJUH. Randomization will occur at TJUH, and the study team at Wills Eye Hospital (WEH) will be alerted to the new enrolled participant as well as indicating which arm of the trial the participant was randomized to.

Enrollment onto this study will only occur at TJUH.

4.5 Participant Withdrawal

4.5.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant's participation in the study 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.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Local progression of disease based on eye examination.
- Non-compliance (missed 3 or more scheduled protocol visits, or determined by treating physicians)

4.5.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be given to the full data set that should to be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug.

If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. IT MUST BE A HIGH PRIORITY TO TRY TO OBTAIN AT LEAST SURVIVAL DATA ON ALL SUBJECTS LOST TO FOLLOW-UP AND TO NOTE WHAT METHODS WERE USED BEFORE ONE CAN STATE THE SUBJECT IS

TRULY LOST TO FOLLOW-UP (three phone calls to subject, phone calls to next-of-kin if possible, certified letters).

4.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency, the Investigational New Drug (IND) /Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the

principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5 Study Intervention

5.1 Study Product

intravitreal Aflibercept Injection

5.2 Study Product Description

Aflibercept is a recombinant fusion protein composed of extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. This drug is formulated as an isosmotic solution for intravitreal administration. Aflibercept acts as a decoy receptor that binds VEGF-A and P1GF with higher affinity than their respective natural receptors, and therefore acts to reduce the effects of endogenous VEGF. This drug is FDA-approved for a number of indications including wet macular degeneration, diabetic maculopathy, and macular edema following retinal vein occlusion

5.2.1 Acquisition

The investigational drug will be supplied by the manufacturer, Regeneron.

5.2.2 Formulation, Packaging, and Labeling

2.0 mg aflibercept is formulated as a sterile liquid to a final concentration of 40 mg/mL IAI in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. IAI 2.0 mg study drug will be supplied by Regeneron Pharmaceuticals Inc. in sealed, sterile 3 mL vials with a “withdrawable” volume of approximately 0.5 mL. Vials must be used only once (defined as entered with a needle). The volume of injection will be 0.05 mL for the 2 mg dose. For study drug in vials, the study drug will be withdrawn using aseptic technique.

Study drug will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C (35.6° to 46.4° F). The Investigator, or an approved

representative (e.g. pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C (35.6° to 46.4° F).

When vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

5.2.3 **Product Storage and Stability**

Study drug will be shipped at a temperature of 2° to 8°C (35.6° to 46.4° F) to the Investigational Drug Service (IDS) at regular intervals or as needed during the study. At the end of the study and following drug reconciliation and documentation, all unopened vials of study drug will be destroyed or returned to Regeneron Pharmaceuticals, Inc. or designee. During transportation from IDS to Shields Oncology at Wills Eye Hospital, a temperature of 2° to 8°C (35.6° to 46.4° F) will be maintained.

5.3 **Dosage, Preparation, and Administration**

Route of administration of aflibercept is through intravitreal injection. The dose per injection will be 2mg of active drug in each arm of the study. Frequency of dosing will depend on which arm the patient is randomized to. In arm A, patients will receive a single injection of 2mg intravitreal Aflibercept 4 months after the completion of radiation treatment, and then again every 2 months afterwards, for a total duration of 2 years (11 injections total). In arm B, patients will receive a single injection of 2mg intravitreal aflibercept 4 months after the completion of radiation treatment, and then once every 4 months afterwards, for a total duration of 2 years (6 injections total). After opening the vial, the drug should be administered under aseptic conditions. All injections of intravitreal aflibercept for both arms will occur at Shields Oncology in Wills Eye Hospital.

5.4 **Dose Modifications and Dosing Delays**

Dosage modifications are not allowed. If the patient experiences significant toxicity (grade 4 or 5 per CTCAE v5.0 criteria), the patient will discontinue the study intervention. Should the patient meet any exclusion criteria described in section 4.12 while under treatment, the patient will similarly discontinue study intervention. The patient will continue to proceed with study-described follow-up every 2 months for a total of 2 years and 2 months.

5.5 Study Product Accountability

All drug accountability records will be kept current.

The investigator or delegated personnel will account for all opened and unopened vials of study drug. These records will contain the dates, quantity, and study medication

- dispensed for each patient – or -

- disposed of at the site per the site's SOP for drug disposal.

All accountability records will be made available for inspection by regulatory agency inspectors.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. Drug destroyed on site will be documented in the study files.

5.6 Assessing Participant Compliance with Study Product Administration

Compliance with radiation therapy will be assessed through documentation of any missed treatments or unplanned treatment breaks. Compliance with IAI therapy will be through direct clinic administration of the drug. Missed or refused doses will be documented.

5.7 Concomitant Medications/Treatments

No specific concomitant medications will be routinely administered. Patients may continue to take all of their pre-enrollment medications for any other medical comorbidity, or any new medication which is prescribed to the patient.

5.8 Dietary Restrictions

No specific dietary restrictions are required.

5.9 Study Procedural Intervention(s) Description Radiation Therapy (Plaque brachytherapy)

Isotope utilized: I-125 seeds (model A IaI-125A) from IsoAid (Port Richey, FL). Planning System: EyePhysics

Gold plaque sizes: round plaques: 10 mm to 22 mm; notched: 18 mm, 20 mm, 22 mm. Associated dummy plaques are matched with each gold plaque.

Procedure: The physician evaluates and determines the patient for appropriateness of plaque brachytherapy. Patient's retinal diagram with tumor dimensions, distance from optic disc and fovea will be generated by Ocular Oncology Service at Wills Eye Hospital.

The tumor information will be entered into the EyePhysics planning system. Appropriate plaque size and shape will be determined. The plan will be generated. Plaque is custom made in the radiation lab where seeds are glued on the inner surface of the plaque according to the plan.

The plaques will be implanted by Ocular Oncology Service at Wills Eye Hospital OR (usually on Thursday morning). The patient will be discharged after implant.

Plaque will be removed promptly at prescribed time (within +/- 10% of prescribed dose).

Dose prescribed: 70 Gy (acceptable range: +/-10%) is prescribed to a depth as determined by ocular exams and defined as the apex of the tumor. 2mm circumferential margin and 1mm apical margin are added to the tumor dimensions for adequate treatment coverage over approximately 4 days or approximately 100 hours based on the calculation. The implant may by necessity continue delivering dose for 5-7 days up to 170 hr if clinically indicated. Seed distribution may be full, posterior or radial based on tumor type and location. Doses to following critical structures are calculated: optic disc, fovea, base dose at 1mm depth, lens, retina, opposite retina.

Ideal Normal Tissue constraints: These doses vary widely based on location of plaque to these critical structures. As a result, these are not mandatory.

Optic disc: < 70Gy Fovea: <70Gy

Lens: 20Gy (acceptable based on location of plaque 65Gy) Base dose: < 400Gy

Opposite Retina: <10 Gy

Radiation Therapy: (SRT)

Simulation

Immobilization of the head will be through use of the BrainLab thermoplastic 3- piece mask system. The outer mask will have holes cut out around the bilateral eyes. The patient will undergo CT scan with Linac SRS protocol utilizing a custom localization block attached to the BrainLab CT board. The patient will be instructed to fix their gaze

on an attached LED light source for the duration of the CT scan, and for each treatment. CT simulation therapists will provide this coaching during time of simulation, and the machine therapists will reinforce this coaching at time of each treatment.

Planning

Planning will be performed using 3D-CRT or VMAT/IMRT technique, with prioritization on lowering dose delivered to the optic tract.

- GTV will include all gross tumor. PTV will be a 2mm expansion off the GTV. No CTV will be defined. Prescription dose will be 50 Gy delivered over 5 fractions prescribed to the PTV delivered every other day (acceptable variation: every day treatment). All treatment should finish within 10 days (acceptable range: 14 days)

PTV coverage should be ≥99%.

Critical structures constraints:

Contralateral eye max dose: 10 Gy

Ipsilateral lens mean dose: 20 Gy (acceptable variation: 45 Gy) Brainstem; 20 Gy

Chiasm: 10 Gy

Contralateral optic nerve: 10 Gy

Ipsilateral optic nerve (minus PTV) max dose: 55 Gy (keep it as low as possible)

Treatment setup and delivery

The patient will be setup on the linac treatment couch utilizing the ExacTrac image guidance system to align to the isocenter. The eye camera and gaze- fixation LED light will be turned on and the patient will be instructed to maintain gaze at the light source. The live eye image feed will be verified and monitored on the control panel in real time by both therapists and the treating physician. A cone-beam CT scan will be acquired on the first treatment day to verify set-up accuracy. Once setup is verified, the treatment will start, and the treating physician will monitor the live feed from the eye camera. A manual beam-pause will be issued in the event of gaze deviation, and will be resumed once gaze is refocused.

5.10 **Administration of Procedural Intervention**

Intravitreal Aflibercept therapy

Medication and dosage will be verified by the treating ophthalmologist prior to administration to check for correct dosage label and expiration. Once verified, the patient will undergo intravitreal injection of the drug under sterile conditions by the treating ophthalmologist, per standard protocol of intravitreal drug injection. The first injection of intravitreal aflibercept will occur 4 months after the completion of radiation therapy. The subsequent injection schedule will depend on the randomization arm as detailed in section 5.3 above.

5.11 Procedures for Training of Clinicians on Procedural Intervention

The administration of IAI will follow the policy and procedure guidelines already in practice by the treating ophthalmologist for intravitreal injections. The treating ophthalmologist will be instructed to follow the proper storage and handling guidelines per the manufacturer recommendations as described in section 5.2.2 and 5.2.3 above.

5.12 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

Compliance for both radiation and IAI therapy will be assessed by direct observation of the treating physicians, given the nature of these interventions.

6 Study Schedule

6.1 Pretreatment Period/Screening

- Obtain and document consent from potential participant on study consent form at Radiation Oncology (Thomas Jefferson University Hospital).
- Review medical to determine eligibility based on inclusion/exclusion criteria.
- Obtain pregnancy test via urine or blood b-HCG for women of childbearing potential within 14 days from enrollment.
- Physical examination including eye exam to document baseline vision status, vital signs, and performance status using the KPS.
- Vision status will be obtained during ophthalmic exam, including best corrected visual acuity (BCVA)
- Perform optical coherence tomography (OCT) scan of eye.
- Perform ultrasound of eye (ocular).

- Schedule study visits for individuals who are eligible and available for the duration of the study.
- Provide potential participants with instructions needed to prepare for first study visit
- SOC Labs: complete blood cell count (CBC) with differential, Day -30 to Day-1 of enrollment.
- Review medications the patient is taking

6.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day -30 to D1 prior to treatment)

- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical history, medication history, alcohol, and tobacco use history.
- Obtain randomization results.
- Record results of physical and ocular examinations.

6.3 Treatment Period

Patients will receive radiation treatment in Radiation Oncology at Thomas Jefferson University.

Treatment with IAI and visits with the ophthalmologist will occur at Wills Eye Hospital.

Radiation Treatment: Plaque Brachytherapy or FSRT treatment (50Gy in 10Gy fractions).

- Record adverse events as reported by participant or observed by investigator.
- Plaque brachytherapy, continuously over 4 days (~100 hr), may be up to 7 days as determined by treating physician.
- FSRT will be given, total of 5 treatments, every other day weekdays only (acceptable variation: every day treatment). All treatment should finish within 10 days (acceptable range: 14 days)
- Record participant's compliance with radiation.

2 month follow-up – no Aflibercept.

- Record adverse events as reported by participant or observed by investigator.
- Obtain vital signs, KPS performance status
- Perform physical examination and eye examination (including BCVA)
- Obtain ultrasound of the eye + OCT scan.
- Laboratory assessments as clinically indicated.

Month 4 following RT: Administer 1st intravitreal dose of IAI for both arms.

- Record adverse events as reported by participant or observed by investigator.
- Obtain vital signs, KPS performance status.
- Perform physical examination and eye examination (including BCVA).
- Obtain ultrasound of the eye + OCT scan.
- Laboratory assessments as clinically indicated.
- Record participant's compliance with intravitreal Aflibercept.

Every two months following first Aflibercept injection starting at month 6 post RT and ending at month 24 post RT.(acceptable variation: ±2 weeks)

- Record adverse events as reported participant or observed by investigator.
- Obtain vital signs, KPS performance status
- Perform physical examination and eye examination (including BCVA)
- Obtain ultrasound of the eye + OCT scan.
- Laboratory assessments as clinically indicated.

Patients in Arm A (Aflibercept every 2 months)

- IAI at each visit (month4, 6, 8, 10, 12, 14, 16, 18, 20, 22 ,24)
- Record participant's compliance with intravitreal Aflibercept

Patients in Arm B (Aflibercept every 4 months)

- IAI on month 4, 8, 12, 16, 20, 24 only
- Record participant's compliance with intravitreal Aflibercept

Final assessment (2 months after last Aflibercept injection) All patients (month 26 ± 1 w)

- Record adverse events as reported by participant or observed by investigator.
- Obtain vital signs, KPS performance status
- Perform physical examination and eye examination
- Obtain ultrasound of the eye + OCT scan.
- Laboratory assessments as clinically indicated.

**Patients will be recommended to continue with standard follow-up care with the treating ophthalmologist, including yearly physical exam, ocular exam, and yearly CXR and liver MRI for surveillance. Any local failures, or distant disease recurrence will be documented. Any patient death will also be recorded.

6.4 Withdrawal Visit/Discontinuation of Therapy

If the patient withdraws from the study early, patient should be encouraged to have an exit visit, with the following evaluations offered:

- Record adverse events as reported by participant or observed by investigator.
- Obtain vital signs, KPS performance status
- Perform physical examination and eye examination
- Obtain ultrasound of the eye + OCT scan.
- Laboratory assessments as clinically indicated

7 Study Procedures and Evaluations

7.1 Study Procedures/Evaluations

Medical history: Should be obtained from both the electronic medical record (EMR) as well as from patient interview. Performance status should also be recorded.

Medication history: Should include all medications the patient is currently taking (including prescription and over-the-counter medications). No specific medications are excluded for enrollment onto this study. The patient is not required to take any particular medications on this study, apart from the investigational drug, intravitreal Aflibercept, which will be administered as detailed in section 5 and 6 above.

Physical exam: Should include assessment of the head and neck area, paying attention to any skin changes, swelling, and hair loss due to radiation therapy. Additionally, an eye exam (both eyes) will be performed including assessment of visual acuity, visual fields, conjunctival changes, periorbital edema, dry-eye, and extra-ocular movements.

Radiographic studies: Include OCT scan, and ultrasound of the eye (ocular).

Laboratory studies as clinically indicated.

8 Evaluation of Safety

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in section 8.1.3

8.1.3 **Serious Adverse Events**

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

Criteria for Serious Sight-Threatening Ocular Adverse Events

Criteria for serious sight-threatening ocular AEs include the following:

- AE causes a decrease in BCVA of >30 letters (compared with the most recent assessment of BCVA).
- AE causes a decrease in VA to the level of light perception or worse.
- AE requires surgical intervention (eg, vitreous tap or biopsy with IVT injection of anti-infectives, laser or retinal cryopexy with gas) to prevent permanent loss of sight.

- AE is associated with severe intraocular inflammation (ie, 4 + anterior chamber cell/flare or 4 + vitritis)

- In the opinion of the investigator, AE may require medical intervention to prevent permanent loss of sight

8.2 Safety Assessment and Follow-Up

The PI will follow adverse 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 (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2 Safety Assessment and Follow-Up.

8.3.1 Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)

    a. The event is known to occur with the study intervention.

    b. There is a temporal relationship between the intervention and event onset.

    c. The event abates when the intervention is discontinued.

    d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

    a. There is no temporal relationship between the intervention and event onset.

    b. An alternate etiology has been established.

8.3.2 **Expectedness**

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

8.3.3 **Severity of Event**

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.3.4 **Intervention**

Any intervention implemented to treat the adverse event must be documented for all adverse events.

8.4 **Safety Reporting**

The Thomas Jefferson University clinical team coordinating the trial will be responsible for reporting adverse events and unanticipated problems as described in the following sections.

8.4.1 **Report to the TJU IRB**

8.4.1.1 ***Unanticipated Problems***

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the TJU IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the TJU IRB at the next continuing review.

8.4.1.2 ***Adverse Events***

Grade 1 AEs will be reported to the TJU IRB at the time of continuing review.

Grade 2 AEs will be reported to the TJU IRB at the time of continuing review.

8.4.1.3 ***Serious Adverse Events***

SAEs will be reported to the TJU IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the TJU IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the TJU IRB within 5 working days.

Grade 5 AEs will be reported to the TJU IRB within one working day of knowledge of the event.

All SAEs will be submitted to the TJU IRB at continuing review, including those that were reported previously.

8.4.2 **Reporting to WEH IRB**

8.4.2.1 ***Unanticipated Problems***

Unanticipated problems (UAPs) that pose risk to participants or others, and that are not AEs, will be submitted to the WEH IRB via memo/letter detailing the incident, concerns, and proposed resolution within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the WEH IRB at the next continuing review.

8.4.2.2 ***Adverse Events***

Grade 1 AEs will be reported to the WEH IRB at the time of continuing review. Grade 2 AEs will be reported to the WEH IRB at the time of continuing review.

8.4.2.3 ***Serious Adverse Events***

SAEs occurring outside of Wills Eye Hospital will be reported to WEH IRB via the Form-3A according to the required timeframes described below.

Any serious and unexpected adverse reaction that is probably or definitely related to the research

Grade 3-4 AEs occurring at Wills Eye Hospital must be reported to WEH IRB within 48 hours via Form-3B

Grade 5 AEs that are unanticipated must be reported to WEH IRB within 24 hours via Form-3B

Grade 5 AEs not related to the research must be reported to WEH IRB within 5 days via Form-3B.

All SAEs will be submitted to the WEH IRB at continuing review, including those reported previously.

8.4.3 **Reporting to SKCC DSMC**

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

For expedited reporting requirements, see table below:
DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

8.4.4 Reporting to Funding Sponsor

All reports to the funder will be submitted by the Thomas Jefferson University clinical team.

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to Regeneron within 15 days

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

Deaths

Any AE that results in death is considered an SAE. Deaths that occur from the time the patient signs the ICF until 30 days after dosing will be reported to the appropriate IRB and to Regeneron Pharmacovigilance and Risk Management (or designee) within 24 hours of learning of the death.

Any available autopsy reports and relevant medical reports will be sent to Regeneron Pharmaceuticals, Inc. as soon as possible.

To report an SAE, Regeneron will be contacted at the following:
Medical.safety@regeneron.com

Fax: (914) 345-7476

SAE hotline: (914) 593-1504

Pregnancy and Other Events that Require Accelerated Reporting

The following events will be reported to Regeneron Pharmaceuticals, Inc. within 24 hours of learning of the event:

1. Overdose: Accidental or intentional overdose of the study drug or concomitant medication, whether or not it is considered an AE.

2. Pregnancy: Although it is not considered an AE, the investigator will report to Regeneron Pharmaceuticals, Inc., any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 30 days following the last dose of study drug. The investigator will follow the pregnancy until delivery, or longer. If the pregnancy continues to term (delivery), the health of the infant will also be reported to Regeneron Pharmaceuticals, Inc.

These AEs will be reported to:

Medical.safety@regeneron.com Fax: (914) 345-7476

SAE hotline: (914) 593-1504

Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study will be reported to Regeneron Pharmaceuticals Inc. within 30 days. All SAEs leading to a patient's withdrawal from the study will be reported. To report an SAE, Regeneron will be contacted at the following:

Medical.safety@regeneron.com Fax: (914) 345-7476

SAE hotline: (914) 593-1504

8.4.5 Reporting to FDA

All reports to the FDA will be submitted by the Thomas Jefferson University clinical team. All reports to the FDA will be submitted using the MedWatch 3500A form.

7 Calendar-Day Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of intravitreal Aflibercept. An unexpected adverse event is one that is not already described in the prescribing instruction.

Such reports are to be telephoned or faxed to the FDA within 7 calendar days and Regeneron within 24 hours of first learning of the event. Each telephone call or fax transmission should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of intravitreal Aflibercept. An unexpected adverse event is one that is not already described in the prescribing information.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Regeneron, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

8.4.6 Reporting of Pregnancy

If pregnancy is noted during any part of enrollment from time of screening to time of radiation therapy completion, the patient must be immediately removed from therapeutic intervention and PI must be informed. No information is available regarding safety of IAI in pregnant women or their fetuses. However, per manufacturer recommendations, patients who are breast feeding should not undergo intravitreal Aflibercept therapy as IgG1s may be excreted in breast milk. Additionally, the manufacturer recommends pregnant women not use intravitreal Aflibercept, and that all women of childbearing age agree to use adequate contraception for at least 3 months following last dose of intravitreal Aflibercept.

See Section 8.4.3 for information on how to report pregnancy to Regeneron.

8.5 Halting Rules

Enrollment should be halted if greater than 40% of patients experience treatment related any ≥Grade 3 toxicity and safety review must convene prior to further enrollment.

9 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed

remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

11 Statistical Considerations

11.1 Study Hypotheses

We hypothesize that the percent of patients who experience CTCAE v5.0 grade ≥3 toxicity related to SRT and/or IAI will be significantly lower than 40%.

11.2 Statistical Analysis Plans

For the primary analysis, the null hypothesis that the rate of toxicity related to radiation and/or IAI is 40% will be tested using one-sided exact binomial test with alpha 0.05. Since the primary endpoint is patient tolerability, the two arms will be combined for the primary analysis. For the secondary analysis, the 2-year rates of radiation maculopathy, radiation papillopathy, functional vision preservation (in pts with functional vision prior to study treatment), radiation glaucoma, and local control will be estimated separately in each arm with the corresponding exact binomial 90% confidence interval. The progression-free survival in the combined two arms of the study will be analyzed using the Kaplan-Meier estimator.

It is not expected that two dosing regimens would produce different levels of toxicity. However, to evaluate this possibility, the rate of toxicity with the corresponding exact binomial 90% confidence interval will be also estimated separately in each arm.

11.3 Sample Size Considerations

The sample size of 33 patients provides 80% to reject the null hypothesis that toxicity rate is 40% if the true toxicity rate is 20%, assuming the one-sided exact binomial test with alpha 0.05. A total of 36 pts will be enrolled to account for drop off and unanalyzable subjects.

11.3.1 Replacement Policy

Patients prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable patients. The investigator, (in cooperation with the study statistician, if applicable) will decide whether or not to replace withdrawn patients.

Patient withdrawn before finishing FSRT and first injection of intravitreal aflibercept will be replaced.

11.3.2 Accrual Estimates

2 pts a month

12 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 Quality Control and Quality Assurance

The investigator will allocate adequate time for monitoring activities by the TJU SKCC. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

14 Ethics/Protection of Human Participants

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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 in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical

care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

Regeneron will have the right to review and comment on the informed consent form.

14.4 **Exclusion of Women, Minorities, and Children (Special Populations)**

This study is intended to investigate treatment outcomes of adults with uveal melanoma, and therefore children (age <18 years) are excluded from this study. No minority group is excluded from this study. Both men and women are eligible for enrollment, however, pregnant or breast-feeding women are excluded due to concern for risk to fetus.

14.5 **Participant Confidentiality**

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

14.6 **Certificate of Confidentiality**

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14.7 **Future Use of Stored Specimens and Other Identifiable Data**

The collected data will be analyzed at end of the study for publication.

15 **Data Handling and Record Keeping**

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

The data will be entered into REDCap on password protected computers on internal network drives. Full imaging reports will remain as part of the EMR, however, documentation of disease and treatment related AEs will be coded into RedCap.

The data will be entered into RedCap by the Thomas Jefferson University clinical team.

15.1 **Data Management Responsibilities**

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2 **Data Capture Methods**

As noted in section 15.1, data will be recorded and stored in RedCap on a password protected internal network drive. Data will be entered into RedCapat the end of each patient follow-up visit or when results from any relevant imaging return.

15.3 **Types of Data**

Data that will be collected will include: Safety (CTCAE v5.0 toxicity data); KPS performance status; physical exam findings including skin/periocular reactions and vital signs; ocular exam findings including visual acuity and visual field testing; imaging reports from OCT scan, and eye ultrasounds.

15.4 **Study Records Retention**

Study records will be maintained for at least 5 years after completion of study.

15.5 **Protocol Deviations**

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

16 Study Finances

16.1 Funding Source

Regeneron is providing a grant and study drug to Wills Eye and Thomas Jefferson University.

16.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

16.3 Participant Stipends or Payments

Participants will not receive any payment for participation in this study.

17 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is

sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

18 Literature References

1. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol. 2017;11:279-89.
2. Shields CL, Kaliki S, Furuta M, Mashayekhi A, Shields JA. Clinical spectrum and prognosis of uveal melanoma based on age at presentation in 8,033 cases. Retina. 2012;32(7):1363-72.
3. Schwartz LH, Ferrand R, Boelle PY, Maylin C, D'Hermies F, Virmont J. Lack of correlation between the location of choroidal melanoma and ultraviolet-radiation dose distribution. Radiat Res. 1997;147(4):451-6.
4. Weis E, Shah CP, Lajous M, Shields JA, Shields CL. The association of cutaneous and iris nevi with uveal melanoma: a meta-analysis. Ophthalmology. 2009;116(3):536-43 e2.
5. Eskelin S, Kivela T. Mode of presentation and time to treatment of uveal melanoma in Finland. Br J Ophthalmol. 2002;86(3):333-8.
6. Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. Archives of ophthalmology. 1990;108(9):1268-73.
7. Collaborative Ocular Melanoma Study G. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the

Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. Archives of ophthalmology. 2001;119(5):670-6.
8. Finger PT, Kurli M, Reddy S, Tena LB, Pavlick AC. Whole body PET/CT for initial staging of choroidal melanoma. Br J Ophthalmol. 2005;89(10):1270-4.
9. Dithmar S, Diaz CE, Grossniklaus HE. Intraocular melanoma spread to regional lymph nodes: report of two cases. Retina. 2000;20(1):76-9.
10. Shields CL, Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR, et al. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Archives of ophthalmology. 2009;127(8):989-98.
11. Collaborative Ocular Melanoma Study G. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. Archives of ophthalmology. 2006;124(12):1684-93.
12. Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, et al. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. Archives of ophthalmology. 2005;123(12):1639-43.
13. American Brachytherapy Society - Ophthalmic Oncology Task Force. Electronic address pec, Committee AO. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy. 2014;13(1):1-14.
14. Gragoudas ES, Goitein M, Verhey L, Munzenreider J, Urie M, Suit H, et al. Proton beam irradiation of uveal melanomas. Results of 5 1/2-year study. Archives of ophthalmology. 1982;100(6):928-34.
15. Gragoudas ES, Lane AM, Regan S, Li W, Judge HE, Munzenrider JE, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. Archives of ophthalmology. 2000;118(6):773-8.
16. Sikuade MJ, Salvi S, Rundle PA, Errington DG, Kacperek A, Rennie IG. Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma. Eye (Lond). 2015;29(9):1194-8.
17. Furdova A, Sramka M, Chorvath M, Kralik G, Krasnik V, Krcova I, et al. Stereotactic radiosurgery in intraocular malignant melanoma--retrospective study. Neuro Endocrinol Lett. 2014;35(1):28-36.
18. Shah SU, Shields CL, Bianciotto CG, Iturralde J, Al-Dahmash SA, Say EA, et al. Intravitreal bevacizumab at 4-month intervals for prevention of macular edema after plaque radiotherapy of uveal melanoma. Ophthalmology. 2014;121(1):269-75.
19. Mashayekhi A, Rojanaporn D, Al-Dahmash S, Shields CL, Shields JA. Monthly intravitreal bevacizumab for macular edema after iodine-125 plaque radiotherapy of uveal melanoma. European journal of ophthalmology. 2014;24(2):228-34.
20. Karagiannis D, Kontomichos L, Georgalas I, Peponis V, Antoniou E, Parikakis E. Glioma-associated radiation retinopathy treated successfully with aflibercept. Ther Clin Risk Manag. 2019;15:937-41.

21. Pooprasert P, Young-Zvandasara T, Al-Bermani A. Radiation retinopathy treated successfully with aflibercept. BMJ Case Rep. 2017;2017.
22. Fallico M, Reibaldi M, Avitabile T, Longo A, Bonfiglio V, Chronopoulos A, et al. Intravitreal aflibercept for the treatment of radiation-induced macular edema after ruthenium 106 plaque radiotherapy for choroidal melanoma. Graefes Arch Clin Exp Ophthalmol. 2019;257(7):1547-54.

Appendices

The following documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

Appendix A: Schedule of Events

Appendix B: KPS Score

APPENDIX A: SCHEDULE OF EVENTS

Procedures	**Screening (D -30 to -1)**	**Visit 1 RT[1]**	**Visit 2 M2[3]**	**Visit 3 M4[3]**		**Visit 4-13 M6 – 24[3]**	**Visit 14 M26[3, 9]**	**Withdrawal Visit/ Discontinuation of Therapy**
Signed Informed Consent[8]	X							
Eligibility and Randomization[8]	X							
Review of Medical History[5]	X							
Physical Exam including vital signs	X		X	X		X	X	X
Karnofsky Performance Status	X		X	X		X	X	X
Ophthalmic Exam (including BCVA)	X		X	X		X	X	X
Ocular Ultrasound	X		X	X		X	X	X
OCT	X		X	X		X	X	X
Review of Concomitant Medications[10]	X	X	X	X		X	X	X
Adverse Events Assessment		X	X	X		X	X	X
CBC w/diff	X[7]						X	
CMP, LFTs							X	
Pregnancy Test (for WOCBP only)[6]	X							
Radiation Treatment (FSRT or Plaque brachytherapy)[1]		X						
IAI (Arm A)[2]				X[11]		X		
IAI (Arm B)[4]				X[11]		X		

Note: BCVA – best corrected visual acuity.

1. FSRT, total of 5 treatments, every other day, weekdays only (acceptable variation: every day treatment). FSRT should finish within 10 days (acceptable range: 14 days). Plaque brachytherapy: total implant time is 4 days (~100 hr up to 170 hr), may be up to 7 days per treating physician.
2. Months 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 after finishing SRT, acceptable variation ±1 weeks.
3. Acceptable variation ± 2 weeks.
4. Months 4, 8, 12, 16, 20, 24, after finishing SRT, acceptable variation ±1 weeks
5. Medical history includes demographics, alcohol use, and tobacco use.
6. Blood or urine pregnancy test must be done within 14 days of enrollment.
7. Screening labs must be done within 30 days of enrollment.
8. Informed Consent and confirmation of eligibility will only occur at Radiation Oncology at Thomas Jefferson University Hospital.
9. Patients will be recommended to continue with standard follow-up care with the treating ophthalmologist, including yearly physical exam, ocular exam, and yearly CXR and liver MRI for surveillance. Any local failures, or distant disease recurrence will be documented. Any patient death will also be recorded.
10. Must include all medications that patient is currently taking (including prescription and over-the-counter medications).
11. Arm A & B: Administer 1st intravitreal dose of Aflibercept 4 months after radiation (acceptable variation ± 2 weeks.)

APPENDIX B: KPS SCORE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalisation is indicated, although death not imminent
20	Very sick; hospitalisation necessary; active support treatment is necessary
10	Moribund; fatal processes
0	Dead