Alliance A071101

Parisa Mirzadehgan, MPH, CCRP

Background

- Approved therapy for a newly diagnosed GBM patient includes
  - surgical resection → radiation & temozolomide
- Upon recurrence there are few approved options
  - surgical implantation of chemotherapy bearing wafers
    - polifeprosan 20 with carmustine implant, Gliadel® Wafer
  - systemic administration of the anti-angiogenic agent bevacizumab
  - Has shown a partial response rate of 20% in one trial, and 26% in another

Rationale

- No approved adjuvant treatments in recurrent GBM that significantly extend survival
- Whether an autologous active immunotherapy, HSPPC-96, used as an adjuvant treatment to surgery and in combination (either concomitantly post-surgery or serially at the point of progression) with the best available and approved therapy, bevacizumab, can extend overall survival

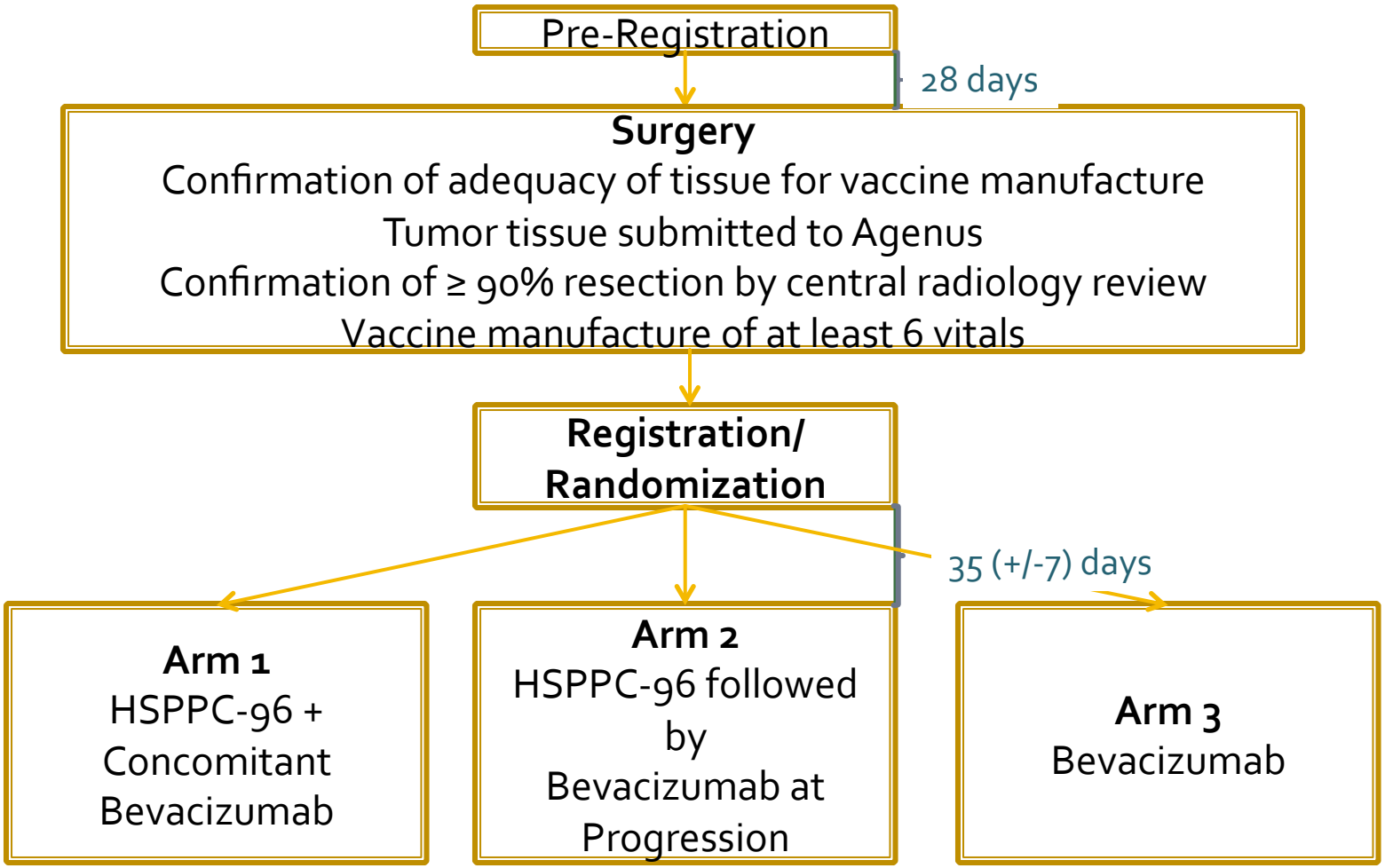
Rationale

- Better characterize the effect of bevacizumab on overall survival in a randomized, controlled setting
- It will also advance the biological understanding of a vital area of cancer research

Rationale

- Provides the opportunity to advance the understanding of cancer vaccines and combination therapy
- Implications for utility of HSPPC-96 in surgically resectable newly diagnosed GBM
- Could also open additional avenues of research with HSPPC-96 and bevacizumab in other cancer indications

Schema


Pre-Registration
28 days
Surgery
Confirmation of adequacy of tissue for vaccine manufacture
Tumor tissue submitted to Agenus
Confirmation of ≥ 90% resection by central radiology review
Vaccine manufacture of at least 6 vitals
Registration/ Randomization
35 (+/-7) days
Arm 1
HSPPC-96 + Concomitant Bevacizumab
Arm 2
HSPPC-96 followed by Bevacizumab at Progression
Arm 3
Bevacizumab

Primary Objective

- To determine whether there is an overall survival advantage of HSPPC-96 administered with bevacizumab, given concomitantly or at the point of progression, in comparison with bevacizumab alone in patients with surgically resectable recurrent GBM

Secondary Objectives

- To evaluate the safety and tolerability of HSPPC-96 with bevacizumab
- To evaluate the progression free survival of HSPPC-96 with bevacizumab, given concomitantly or at the point of progression

Correlative Science Objectives

- To evaluate whether patients who demonstrate an immune response to HSPPC-96 will have an improved survival outcome in comparison to those patients who do not show immune response
- To explore whether T-cell infiltrate of tumor at baseline correlates with response to vaccine

Pre-registration Eligibility Criteria

- Prior histologic diagnosis of GBM at first occurrence
- First or second recurrence of GBM considered to be surgically resectable
- No radiotherapy within 90 days prior to pre-registration
- No prior treatment with any anti-angiogenic agent targeting the VEGF pathway including:
  - bevacizumab, cediranib, vandetanib, sunitinib, pazopanib, aflibercept or sorafenib
- No prior treatment with HSPPC-96 or other investigational immunotherapy
- Must have received prior treatment with radiotherapy and temozolomide for histologically confirmed GBM at initial diagnosis
- No tumor directed therapy for most recent progression
- No prior Gliadel® wafers

Pre-registration Eligibility Criteria

- No clinically significant cardiovascular disease
- No significant bleeding within the past 6 months; no bleeding diathesis or coagulopathy
- No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within past 12 months
- No evidence of any systemic autoimmune disease (e.g. Hashimoto's thyroiditis) and/or any history of primary or secondary immunodeficiency, and no immunosuppressant therapy (with the exception of dexamethasone as noted below) for any reason
- Age ≥ 18 years of age
- Karnofsky functional status rating ≥70
- No more than 16 mg dexamethasone (or equivalent) per day
- Non-pregnant and non-nursing

Registration Eligibility Criteria

- Confirmed histological diagnosis of recurrent GBM
- ≥ 90% surgical resection of recurrent GBM confirmed by central radiology review by MRI with or without gadolinium per institutional guidelines
  - A CT scan is allowable in place of MRI only in situations where an MRI is contraindicated (e.g., patient has a heart pacemaker, metallic devices in the eye, brain or spine, severe claustrophobia)
- ≥ 7 grams of resected tumor available for vaccine manufacture as determined by institutional pathologist
- Availability of ≥ 6 clinical vials of HSPPC-96

Registration Eligibility Criteria

- No serious, non-healing wounds or ulcers
- At least 7 days since any minor surgery such as port placement
- No major surgical procedures, open biopsy or significant traumatic injury ≤28 days prior to registration or anticipation of need for elective or planned major surgical procedure during the study
  - Core biopsy or other minor surgical procedures ≤7 days prior to registration
- No active or recent hemoptysis (≥½ teaspoon of bright red blood per episode) ≤30 days prior to registration
- No new bleeding on D28 (+/-3) MRI (or CT if MRI is contraindicated)
- No clinical deterioration at the time of registration/randomization
- If a second surgery is needed for completion of resection, this should be within 30 days from the first surgery

Pre-registration Requirements

- Institutions MUST contact the Study Chair at the phone number or email address listed on the protocol cover page immediately upon IRB approval for site qualification and to identify the neurosurgeon
- Failure to contact the Study Chair will result in the inability to pre-register patients

Registration Procedures

- Confirmation must be sent from site to Agenus informing Agenus that tumor material for a patient is being shipped to attempt vaccine manufacture
  - The Tissue Procurement Form (TPF) must be completed and faxed to Agenus as per the instructions on the TPF. Sites can obtain the study-specific TPF from the CTSU website.
- Bulk tumor tissue must be sent from site to Agenus for vaccine manufacture
  - The completed Tissue Procurement Form (TPF) must be included with the tissue sent to Agenus
- Notification must be sent to Agenus that ≥ 90% surgical resection of recurrent GBM has been confirmed by the Alliance Imaging Core Lab central radiology review

Registration Requirements

- Receipt by site of the designated Vaccine Production Notification Form from Agenus, which will inform the site of the status of the HSPPC-96 vaccine
  - If successfully produced, the number of available vials that will be shipped along with the anticipated shipping date
  - within 14 days of receiving the tumor material for processing
- At least 6 clinical vials
- If the patient is not eligible to participate, the Vaccine Order Form MUST be faxed to Agenus
  - The site should check "No, please do not ship vaccine (Arm 3 or other reason) and identify in the comments section that the patient is a screen failure

Patient Registration/ Randomization

- Patients should be randomized 48 to 72 hours after receipt of Vaccine Product Notification Form from Agenus
  - After randomization, sites must complete the Vaccine Order Form and fax or email it to Agenus in order to have vaccine shipped
- The site staff will enter the patient ID number obtained at pre-registration and the patient's age stratum and KPS stratum

Registration to Sub-studies

- Will be done at the same time as registration to the treatment study
- One sub-study:
  - **A071101-ST1**: Correlative Science in A071101
  - This study **must be offered to all patients** enrolled on A071101
- If a patient answers "yes" to model consent question #1, they have consented to participate in the sub-study

Surgical Quality Assurance

- It is recommended that the neurosurgeon has performed at least 20 brain tumor resections over the last 12 months
- The neurosurgeon does not need to hold a Cooperative Group membership

Tissue Kits

- Kits for shipping tissue will be supplied by Agenus and should be ordered at time of IRB submission because they will be needed at time of surgery