

**APPENDIX: PBTC-061: Phase 2 Trial of G207 + 5 Gy Radiation for Children with High-Grade Gliomas**

**Standard Brain MR Imaging:**

The specific acquisition parameters, the sequence of imaging acquisition, and the plane of imaging are all required as stated in these protocols. Additionally, individual patients must be consistently imaged at the same field strength as their baseline registration scan. Additional sequences that the site wants can be added prior to injection or after the 3DT1 post but the time between injection and the 3DT1 post must be the same for each scan.

All MRI scans for every patient for the duration of the study are to be transferred to the PBTC Operations, Biostatistics and Data and Management Core at St. Jude Children’s Research Hospital and then to the PBTC Neuroimaging Center.

Any questions, please contact Tina Young Poussaint, MD, FACR, Department of Radiology, Boston Children’s Hospital, [tina.poussaint@childrens.harvard.edu](mailto:tina.poussaint@childrens.harvard.edu), 617-355-6450.

**3T Protocol:**

|                     | Ax FLAIR                                  | Ax DWI  | 3D T1 Pre                 | Ax T2                | Contrast Injection <sup>a</sup> | 3D T1 Post                    | Ax FLAIR                                  |
|---------------------|---|---|---------------------------|----------------------|---------------------------------|-------------------------------|---|
| Sequence            | TSE/FSE <sup>b</sup> – (turbo dark fluid) | EPI   | SPACE <sup>c</sup>        | TSE/FSE <sup>b</sup> |                                 | SPACE/Cube/VISTA <sup>c</sup> | TSE/FSE <sup>b</sup> – (turbo dark fluid) |
| Plane               | Axial                                     | Axial   | Axial/Sagittal            | Axial                |                                 | Axial/Sagittal                | Axial                                     |
| Mode                | 2D  | 2D  | 3D                        | 2D                   |                                 | 3D                            | 2D  |
| TR [ms]             | >6000                                     | >5000   | 2100 <sup>e</sup>         | >2500                |                                 | 2100 <sup>e</sup>             | >6000                                     |
| TE [ms]             | 100-140                                   | Min   | Min                       | 80-120               |                                 | Min                           | 100-140                                   |
| TI [ms]             | 2500                                      |   | 1100 <sup>f</sup>         |                      |                                 | 1100 <sup>f</sup>             | 2500                                      |
| Flip Angle          | 90/≥160                                   | 90/180  | 10-15                     | 90/≥160              |                                 | 10-15                         | 90/≥160                                   |
| Frequency           | ≥256                                      | 128   | 256                       | ≥256                 |                                 | 256                           | ≥256                                      |
| Phase               | ≥256                                      | 128   | 256                       | ≥256                 |                                 | 256                           | ≥256                                      |
| NEX                 | ≥1  | ≥1  | ≥1                        | ≥1                   |                                 | ≥1                            | ≥1  |
| Frequency Direction | A/P                                       | R/L   | A/P                       | A/P                  |                                 | A/P                           | A/P                                       |
| FOV <sup>g</sup>    | 240mm                                     | 240mm   | 256mm (for 1mm isotropic) | 240mm                |                                 | 256mm (for 1mm isotropic)     | 240mm                                     |
| Slice Thickness     | ≤4mm                                      | ≤4mm  | 1mm <sup>g</sup>          | ≤4mm                 |                                 | 1mm <sup>g</sup>              | ≤4mm                                      |
| Gap/Spacing         | 0   | 0   | 0                         | 0                    |                                 | 0                             | 0   |
| Diffusion Options   |   | <i>b</i> = 0 and 1000 s/mm <sup>2</sup> ≥3 directions |                           |                      |                                 |                               |   |
| Parallel Imaging    | Up to 2x                                  | Up to 2x  | Up to 2x                  | Up to 2x             |                                 | Up to 2x                      | Up to 2x                                  |
| Scan Time (Approx)  | 4-5 min                                   | 3-5 min   | 5-8 min                   | 3-5 min              |                                 | 5-8 min                       | 4-5 min                                   |

**Please add Ax SWI/VENBOLD/SWAN, Acquisition mode: 3D; 1 mm<sup>3</sup> isotropic, 4mm skip 0.**

- <sup>a</sup> 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
- <sup>b</sup> TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
- <sup>c</sup> SPACE= Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (Siemens) is equivalent to Cube (GE) and VISTA=Volume Isotropic Turbo spine echo Acquisition (Phillips)
- <sup>d</sup> MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
- <sup>e</sup> For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
- <sup>f</sup> For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
- <sup>g</sup> FOV and matrix size should be chosen to keep resolution at 1mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions. *Smaller FOV (200mm) may be required for smaller head sizes (young child vs adolescent)*

#### Acronyms:

Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view; SPACE= Sampling Perfection with Application optimized Contrasts using different flip angle Evolution; VISTA=Volume Isotropic Turbo spine echo Acquisition.

#### MRI Permeability and Perfusion Imaging:

The perfusion protocol will be performed using T1-weighted dynamic contrast-enhanced (DCE) permeability MRI to assess immediate biological activity followed by T2\*-weighted dynamic susceptibility contrast (DSC) perfusion MRI technique. DSC perfusion MRI dynamics will allow assessment of the hemodynamic parameter relative cerebral blood volume (rCBV). DCE permeability MRI metrics will include the volume transfer constant between plasma and extravascular extracellular space ( $k^{\text{trans}}$ ), fractional blood-plasma volume ( $V_p$ ), and the volume of the extravascular extracellular space per unit volume tissue ( $V_e$ ). Both DCE and DSC MRI-derived data will be complementary to conventional contrast-enhanced MR imaging.

#### *DCE permeability MRI*

Please note that there will be a total of 5 sequences: 4 for T1 mapping and the DCE with injection). A 3D (not 2D) fast gradient echo type of sequences (fast SPGR, FLASH, THRIVE) must be used. This will be performed as 3D slab in the axial plane. Normalization or intensity correction or flow correction filters such as CLEAR, SCIC or PURE must not be used for any of the series. The slice locations and positioning for the T1 mapping and the dynamic series *MUST* be identical (same matrix, slices, FOV, TR, TE, except NEX and FA). Hence copying of the slices is needed. The TR and TE for all 4 series (4 T1 maps plus a dynamic series) should be identical. For GE systems, reduce Turbo Factor to 1 or 0 if TR and TE do not

match across series. T<sub>1</sub> Maps should be acquired with 2 signal averages and the Dynamic Series with 1. Temporal Resolution of “T<sub>1</sub> DCE” series (scan time per phase/measurement) *should be less than or equal to 6 Seconds, with NO gaps between phases.*

ASSET/IPAT/Parallel Imaging Parallel imaging is set to be OFF, however, if it is not possible to achieve a temporal resolution of less than 6 seconds, this should be set to a factor of 2. The dynamic series should last 5 minutes in total scan time (*excluding T<sub>1</sub> mapping series*).

The table below describes the image acquisition parameters for the T<sub>1</sub> map sequences as well as the dynamic scan, ***in the order of acquisition (first T<sub>1</sub> maps then T<sub>1</sub> DCE)***. Make sure this happens ***before*** DSC perfusion MRI.

The first half dose of contrast agent to be administered 20 sec into “T<sub>1</sub> DCE” sequence. Do NOT inject prior to T<sub>1</sub> DCE or during T<sub>1</sub> maps (see tables 1 and 2 below).

| <b>Series Name</b> | <b>Sequence</b>             | <b>Flip Angle</b> | <b>Notes</b>                          |
|--------------------|-----------------------------|-------------------|---------------------------------------|
| T1 map15           | 3D fast GRE                 | 15 degrees        | Axial, 2 NEX                          |
| T1 map10           | 3D fast GRE                 | 10 degrees        | Axial, 2 NEX                          |
| T1 map05           | 3D fast GRE                 | 5 degrees         | Axial, 2 NEX                          |
| T1 map02           | 3D fast GRE                 | 2 degrees         | Axial, 2 NEX                          |
| T1 DCE             | Dynamic Series, 3D fast GRE | 15 degrees        | Axial, 1 NEX, inject 20 sec into this |

|  |  |
|--|--|
| Sequence type                                | Spoiled gradient echo                                  |
| Imaging mode                                 | <b>3D</b>  |
| Slice orientation                            | Axial  |
| Frequency direction                          | A/P  |
| Phase direction                              | R/L  |
| FOV - frequency                              | 220 mm   |
| FOV - phase                                  | 220 mm   |
| Matrix - frequency                           | 256  |
| Matrix - phase                               | 160-192  |
| In-plane resolution                          | ≤ 1 mm   |
| Fat-suppression                              | No Fat Sat   |
| TR   | ~4 msec  |
| TE   | Less than 2 ms or min full                             |
| TI (STIR sequence)                           | N/A  |
| Flip Angle                                   | DCE -15 degrees; T <sub>1</sub> maps - 2, 5, 10 and 15 |
| Slice thickness (acquired, not interpolated) | 5mm, maximum 6mm                                       |
| Number of slices                             | Minimum 10 prior to zero fill                          |
| Slice Gap                                    | No gap   |
| Parallel imaging factor                      | ≤ 2  |
| Number of averages                           | 1 for DCE, 2 for T <sub>1</sub> maps                   |
| k-space ordering                             | standard, non-centric                                  |

|  |             |
|--|-------------|
| Temporal Resolution of “T1 DCE”: (seconds per phase/measurement) | ≤ 6 seconds |
| “T1 DCE” imaging duration  | ≥ 5 minutes |

Run the Dynamic multi-phase “T1 DCE” at flip angle of 15 degrees – enable multi-phase (on GE systems) and increase the number of phases (or measurements) until the scan time is **six** minutes. Contrast injection should be delivered at 20 sec into T1 DCE, not earlier. Injection rate is 2 ml/second at 0.05 mmol/kg body weight followed by a 10 cc saline flush at the same rate (all should use the same type of contrast agent).

*Diffusion imaging*

Diffusion imaging or axial T2 weighted imaging can be performed between the DCE and DSC MRI acquisitions. In addition to providing permeability metrics, the gadolinium contrast agent from the DCE acquisition will also serve as a “preload” to help correct for leakage effects for the DSC perfusion acquisition.

*DSC perfusion MRI*

An axial 2D T2\* GRE-EPI sequence will be used. TR = 2000 ms, TE = 23 ms, matrix = 128 x 128, FOV = 240 mm, frequency direction R-L, slice thickness = 5.0 mm with 2 mm gap, flip angle = 60 degrees, NEX = 1. Repeat 50-60 times. Total acquisition time ~ 2 minutes. Begin bolus injection (2 ml/sec) of 0.05mmol/kg BW GdDTPA at 20secs after scanning starts followed by a 10 cc saline flush at the same rate. Regional rates of transverse relaxation enhancement ( $\Delta R2^*$ ) during contrast agent passage will be calculated from:  $\Delta R2^*(t) = (-1/TE) \ln [S(t)/S(0)]$  from which estimates of rCBV will be derived.