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

All sequences in this imaging protocol are required.

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:

- Asim Bag, MBBS, MD, Department of Diagnostic Imaging, St. Jude Children's Research Hospital, asim.bag@stjude.org, 901-595-3347; and
- Tina Young Poussaint, MD, FACR, Department of Radiology, Boston Children's Hospital, tina.poussaint@childrens.harvard.edu, 617-355-6450.

3T Protocol:

	Ax FLAIR[h]	Ax DWI	3D T1 Pre [c,i,j]	Ax T2[k]		3D T1 Post [c,i,j]	Ax FLAIR
Sequence	TSE/FSE[b] – (turbo dark fluid)	EPI	MPRAGE or SPACE/CUBE /VISTA	TSE/FSE[b]		MPRAGE or SPACE/Cube/VISTA	TSE/FSE[b] – (turbo dark fluid)
Plane	Axial	Axial	Axial/Sagittal	Axial		Axial/Sagittal	Axial
Mode	2D	2D	3D	2D		3D	2D
TR [ms]	>6000	>5000	2100[e,j]	>2500		2100[e, j]	>6000
TE [ms]	100-140	Min	Min	80-120		Min	100-140
TI [ms]	2500		1100[f, j]			1100[f, j]	2500
Flip Angle	90/^{3}160	90/180	10-15[j]	90/^{3}160		10-15	90/^{3}160
Frequency	^{3}256	128	256	^{3}256		256	^{3}256
Phase	^{3}256	128	256	^{3}256		256	^{3}256
NEX	^{3}1	^{3}1	^{3}1	^{3}1		^{3}1	^{3}1
Frequency Direction	A/P	R/L	A/P	A/P		A/P	A/P
FOV[g]	240mm	240mm	256mm (for 1mm isotropic)	240mm		256mm (for 1mm isotropic)	240mm
Slice Thickness	≤4mm	≤4mm	1mm[g]	≤4mm		1mm[g]	≤4mm
Gap/Spacing	0	0	0	0		0	0
Diffusion Options		*b* = 0 and 1000 s/mm^2 ≥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

Contrast Injection [a]

Ax SWI/VENBOLD/SWAN, Acquisition mode: 3D; 1 mm^3 isotropic.

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
[b] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[c] 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)
[d] 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).
[e] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[f] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[g] 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)*
[h] The pre-contrast FLAIR is optional
[i] **The pre- and post contrast 3D T1 acquisitions need to be identical to generate subtraction maps**.
[j] **T1 SPACE/CUBE/VISTA is preferred over MPRAGE.** For T1 SPACE/CUBE/VISTA please use this parameter: TR: ~900 ms; TE: minimum, TI: NA; Flip angle: variable
[k] The T2 can be performed between permeability and perfusion imaging.

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^{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). If possible, the patient should be scanned on the same scanner for subsequent scans. 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 T_1 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 T_1 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_1 Maps should be acquired with 2 signal averages and the Dynamic Series with 1. Temporal Resolution of "T1 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* T1 mapping series).

The table below describes the image acquisition parameters for the T_1 map sequences as well as the dynamic scan, ***in the order of acquisition (first T1 maps then T1 DCE)***. Make sure this happens ***before*** DSC perfusion MRI.

The first half dose of contrast agent to be administered 20 sec into "T1 DCE" sequence. Do NOT inject prior to T1 DCE or during T1 maps (see tables 1 and 2 below).

Table 1: "T1 DCE"			
Series Name	**Sequence**	**Flip Angle**	**Notes**
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

Table 2:3D T1W specs for T_1 Maps and Dynamic Series	
Sequence type	Spoiled gradient echo
Imaging mode	**3D**
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; T1 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 T1 maps
k-space ordering	standard, non-centric
Temporal Resolution of "T1 DCE": (seconds per phase/measurement)	£ 6 seconds
Number of dynamics	60
Contrast injection time	At the start of the 6th dynamics
"T1 DCE" imaging duration	³ 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 the follow-up scans should use the same type of contrast agent**).

DSC perfusion MRI:

An axial 2D T2* GRE-EPI sequence will be used. TR = 1000-1500 ms, TE = 23 ms, matrix = 128 x 128, FOV = 240 mm, frequency direction R-L, slice thickness = 4.0 mm with no gap, flip angle = 60 degrees, NEX = 1. Repeat 75 times. Begin bolus injection (2 mL /sec) of 0.05mmol/kg body weight (the second half dose) at beginning of 12th dynamics followed by a 10 cc saline flush at the same rate. Regional rates of transverse relaxation enhancement (ΔR2*) during contrast agent passage will be calculated from: ΔR2*(t) = (-1/TE) In [S(t)/S(0)] from which estimates of rCBV will be derived.