Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials neuroimaging endpoint workshop (January 30, 2014, Bethesda MD)

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On January 30, 2014, a workshop was held on neuroimaging endpoints in high-grade glioma. This workshop was sponsored by the Jumpstarting Brain Tumor Drug Development Coalition, consisting of the National Brain Tumor Society, the Society for Neuro-Oncology, Accelerate Brain Cancer Cure, and the Musella Foundation for Research and Information, and conducted in collaboration with the Food and Drug Administration. The workshop included neuro-oncologists, neuroradiologists, radiation oncologists, neurosurgeons, biostatisticians, patient advocates, and representatives from industry, clinical research organizations, and the National Cancer Institute. This report summarizes the presentations and discussions of that workshop and the proposals that emerged to improve the Response Assessment in Neuro-Oncology (RANO) criteria and standardize neuroimaging parameters.

Keywords: brain tumor, endpoints, neuroimaging, RANO, workshop.

High-grade gliomas (HGGs) are the most common type of primary malignant brain tumor, with an annual incidence in the United States of over 15 000 patients.¹ Despite significant progress in understanding the molecular pathogenesis of these tumors^{2–4} and extensive efforts at evaluating novel therapeutic agents, there has been only minimal progress in developing more effective therapies.^{5,6} With the exception of the introduction of temozolomide for patients with newly diagnosed glioblastoma (GBM)⁷ and recurrent anaplastic gliomas,⁸ bevacizumab for patients with recurrent GBM,^{9,10} and procarbazine/lomustine/vincristine chemotherapy for anaplastic oligodendrogliomas,^{11,12} there have been limited advances in the past 15 years (see Table 1 for approved drugs for HGG). Many factors contribute to this lack of progress. These include extensive molecular and cellular tumor heterogeneity, redundant signaling pathways, coactivation of tyrosine kinase receptors, intrinsic resistance to many therapies, poor passage of most therapeutic agents across the blood–tumor barrier, lack of predictive preclinical models, failure to genetically enrich trials of

targeted agents, and a relative lack of interest from pharmaceutical companies because of the poor track record of success and the relatively small patient population.^{13,14}

There is growing consensus that a major limiting factor to developing more effective therapies for HGG is the lack of reliable and widely accepted response criteria and clinical trial endpoints. The Jumpstarting Brain Tumor Drug Development Coalition, consisting of the National Brain Tumor Society, the Society for Neuro-Oncology, Accelerate Brain Cancer Cure, and the Musella Foundation for Research and Information, is sponsoring workshops to evaluate and improve the use of various endpoints in brain tumor clinical trials. The goal is to advance the development of treatments for brain tumors, with a particular focus on gliomas. These workshops will be conducted in close collaboration with the Food and Drug Administration (FDA) and include neuro-oncologists, neuroradiologists, radiation oncologists, neurosurgeons, biostatisticians, patient advocates, and representatives from industry, clinical research organizations, and the National Cancer Institute (NCI). The goal is to reach

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Table 1. Basis for prior approvals for HGGs

Therapy	Year	Indication	Endpoint
Nitrosoureas	1970s	Primary and metastatic brain tumors	ORR
Gladel wafer (carmustine implant)	1996	Recurrent GBM as adjunct to surgery	OS
	2003	First-line HGG as adjunct to surgery and radiation	OS
Temodar (temozolomide)	1999	Refractory anaplastic astrocytoma (accelerated approval)	Durable ORR
	2005	First-line GBM concomitant with radiotherapy followed by maintenance therapy	OS
Avastin (bevacizumab)	2009	GBM that has progressed following prior therapy (accelerated approval)	Durable ORR

consensus on optimal endpoints and identify critical issues that the field needs to address to improve these endpoints. Ultimately, the goal is to improve clarity and enhance interest in the pursuit of clinical trials that can lead to FDA approval of new therapies.

The first of these workshops was held in Bethesda, Maryland, on January 30, 2014. This workshop focused on the capability of neuroimaging to accurately assess response in HGG and the use of current and emerging imaging-based endpoints in clinical trials. Specifically, participants discussed how to overcome the variables in medical imaging, such as image acquisition parameters, that have hindered the ability to accurately assess brain tumor response to therapies, and how to best incorporate endpoints that rely on imaging into clinical trials.

This report summarizes the presentations and discussions of that workshop and the proposals that emerged to improve the Response Assessment in Neuro-Oncology (RANO) criteria¹⁵ and standardize neuroimaging parameters. In addition, there is an imaging core lab perspective on glioblastoma imaging and response assessment in clinical trials (available as supplementary material).

Workshop Overview

The workshop began with 3 preliminary presentations to establish context for the day's discussions: "Efficacy Endpoints in Glioblastoma Multiforme Clinical Trials—A Regulatory Perspective," "Avastin and the Basis of Approval for GBM in 2009," and "Current Brain Tumor Imaging Protocols in Multicenter Trials." After these presentations, the workshop continued with 4 panel-led discussions. The panels consisted of experts in neuro-oncology and neuroradiology, FDA officials, biostatisticians, and representatives from industry. After a short overview presentation by each panel, a 2-part discussion period followed: (i) response by panelists to central questions posed by the moderator, and (ii) facilitated audience question and answer.

Efficacy Endpoints in Glioblastoma Multiforme Clinical Trials—A Regulatory Perspective. Martha Donoghue, MD, from the Office of Hematology and Oncology Products, FDA, provided an overview of guidelines for regulatory approval of new agents, the strengths and weaknesses of current oncology endpoints, a summary of the 2006 FDA Brain Tumor Clinical Trials Endpoints Workshop, progress in imaging endpoints since then, and considerations for future clinical trials.

Current Guidelines for Regulatory Approval

Approval of a new therapy requires substantial evidence of effectiveness,¹⁶ as demonstrated by adequate and well-controlled

investigation involving one or more studies. For biologics, there should be evidence that a therapy is safe, pure, and potent. Regular approval requires substantial evidence of clinical benefit, defined as improvement in how a patient "functions, feels, or survives." Accelerated approval may be given in serious or life-threatening diseases when an improvement is demonstrated over available therapies. Accelerated approval may be based on a surrogate endpoint that is reasonably likely to predict clinical benefit. Surrogate endpoints may include progression-free survival (PFS) and durable tumor shrinkage (objective response rate [ORR] plus duration of response). Examples include durable complete response in chronic myelogenous leukemia¹⁷ and durable ORR for vismodegib in patients with unresectable or metastatic basal cell carcinoma.¹⁸ Confirmatory trials are required for conversion to regular approval and should be under way at the time of accelerated approval. Accelerated approval is subject to withdrawal if clinical benefit is not confirmed in postmarketing trials.

Strengths and Weaknesses of Current Oncology Endpoints

Overall survival (OS) (time from randomization until death) has the advantage of being unambiguous, easily quantified, and not subject to investigator interpretation. However, the limitations are that it requires randomized trials, large sample sizes, and long follow-up periods and that crossover from the control to the experimental arm may dilute the overall effect.

PFS (time from randomization to progressive disease or death) has the advantages of a shorter follow-up period compared with OS, the treatment effect is not obscured by subsequent treatment, and it provides a measure of safety because it includes deaths. Limitations include the need for randomized trials, difficulty in reliably assessing progression in some tumors, the requirement for consistent use of assessments at baseline and at regular intervals, and potential for bias.

ORR (percentage with partial or complete response) has the advantage that tumor shrinkage can unequivocally be attributed to treatment in the absence of confounding factors and does not require a randomized trial assuming no response if patients are not treated. However, assessment of response duration is required, and determination of ORR can be difficult in some diseases, including HGG.

Quality of life measures improvement in patient symptoms or function. Its strengths are that it captures the patient's perspective and is a direct measure of clinical benefit. Limitations include the need for validated patient-reported outcome (PRO) instruments, the potential for bias requiring blinded randomized trials, and missing data, which often limits interpretation.

2006 FDA Brain Tumor Clinical Trials Endpoints Workshop

In 2006, the FDA, in conjunction with the American Society for Clinical Oncology and the American Association for Cancer Research, sponsored a public workshop on Brain Tumor Clinical Trial Endpoints.¹⁹ The goal of the workshop was to identify efficacy endpoints that could be incorporated into clinical trials. In particular, the panel was asked to evaluate potential nonsurvival endpoints that may either directly represent clinical benefit or, as potential surrogates, be reasonably likely to predict clinical benefit in primary brain tumors. There was a consensus among panel members that 6-month PFS was an endpoint that should be pursued in trials in the future. It was felt that imaging techniques assessed or predicted progression reasonably well, although there were concerns about reproducibility. They were felt to assess response less well, except in the case of complete responses or a dramatically high response rate. There was also consensus among panel members that PRO metrics were not yet sufficiently developed to be acceptable in registration trials in primary brain tumors.

Progress Since 2006 FDA Brain Tumor Clinical Trials Endpoints Workshop

Since that workshop, many issues still need to be addressed, but improvements in response assessment have occurred with greater standardization of imaging and the introduction of an updated response criteria proposed by the RANO working group.¹⁵ FDA approvals of targeted therapies for treatment of molecularly defined patient subsets have become increasingly common for a variety of cancers and are frequently supported by sustained ORRs or PFS improvements of large magnitude. This highlights the continued importance of radiographic endpoints. In addition, a new regulatory tool termed “Breakthrough Therapy Designation” has been introduced. This (i) requires preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints and (ii) provides for more frequent interaction with FDA throughout the drug development process, along with the benefits of “fast track designation.”

Considerations for Future Clinical Trials

Overall survival remains the gold standard for approval of therapies to treat most primary brain tumors. Interpretation of radiographic response remains challenging in GBM, but these challenges are less important if the treatment effect is large and improvement is demonstrated in other endpoints. Existing endpoints can be used to support approval of GBM therapies, with OS and PRO endpoints using validated instruments for regular approval and PFS and durable ORR of large magnitude for accelerated approval and possibly for regular approval.

Avastin and the Basis of Approval for Glioblastoma Multiforme in 2009

Lee Pai-Scherf, MD, from the Office of Hematology and Oncology Products of the FDA, who was involved in the accelerated approval of bevacizumab for recurrent GBM in 2009, provided an overview and analysis of that process. Bevacizumab was given

accelerated approval for GBM as a single agent for adult patients with progressive disease following prior therapy based on the results of 2 phase II trials, a multicenter study, AVF3708g (BRAIN study),⁹ and an NCI study, 06-C-0064E.¹⁰ The primary regulatory endpoint was ORR, determined by an independent review facility, and the secondary endpoint was duration of response. AVF3708g was a noncomparative randomized phase II study evaluating bevacizumab alone and bevacizumab and irinotecan. In the 85 patients randomized to the bevacizumab alone arm, the FDA-determined response rate using the modified Macdonald criteria²⁰ was 25.9% (95% CI: 15.9, 37.8) and the median duration of response was 4.2 months (95% CI: 3.0, 5.7). In the supporting NCI 06-C-0064E study, an open-label single-arm phase II trial in 56 patients, the FDA determined that ORR was 19.6% (95% CI: 10.9, 31.3) and the median duration of response was 3.9 months (95% CI: 2.3, 17.4). There were no complete responses in either study. The incidence of bevacizumab-induced adverse events was not significantly increased in patients with GBM compared with other studies.

On March 31, 2009, an Oncologic Drugs Advisory Committee meeting was convened to discuss the validity of objective response, as determined by standard MRI in the setting of vascular endothelial growth factor (VEGF) inhibition, to support accelerated approval in GBM. The committee felt that patients with recurrent GBM had few treatment options. They were unsure whether the changes on the radiographic images were due to changes in vascular permeability and/or reduction in tumor. However, committee members felt that the changes resulted in a positive benefit with respect to symptoms based on the decreased steroid requirement and anecdotal reports of symptom improvement. Many committee members felt that any future trials should be powered to measure quality of life. They voted 10 to 0 in support of accelerated approval.

In May 2009, accelerated approval was granted for bevacizumab for GBM based on (i) clinically important durable objective responses in a disease with no other therapeutic options and (ii) responses confirmed by independent radiologic review. There was a commitment to conduct a postmarketing study to confirm the benefit of bevacizumab for full approval (AVF4396g/BO21990: “A Randomized, Double Blind, Placebo Controlled, Multicenter Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, followed by Bevacizumab and Temozolomide Versus Placebo, in Patients with Newly Diagnosed Glioblastoma [AVAglio]).” The results of this study were recently published.²¹

Current Brain Tumor Imaging Protocols in Multicenter Trials

Benjamin Ellington, PhD, from the University of California–Los Angeles provided an overview of current brain tumor imaging used in multicenter trials. He discussed “basic” MRI protocols, including 2-dimensional T2-weighted MRI, T2-weighted fluid attenuated inversion recovery (FLAIR) MRI, diffusion-weighted imaging (DWI), gradient echo/susceptibility-weighted MRI, and pre- and postcontrast T1-weighted MRI. In addition, he discussed “advanced” MRI protocols that may be used in multicenter trials, such as 2D diffusion tensor imaging (DTI), dynamic contrast-enhanced (DCE) perfusion MRI to evaluate vascular permeability, dynamic susceptibility contrast (DSC) perfusion MRI to evaluate cerebral blood volume, and 3D postcontrast T1-weighted MRI.

Summary of Panel Presentations and Discussions

Pros and Cons of Current Brain Tumor Imaging (Panel 1)

(Lauren Abrey, MD, Roche; Timothy F. Cloughesy, MD, UCLA; Ruthann Giusti, MD, FDA; Daniel Krainak, PhD, FDA; Martin van den Bent, MD, Erasmus Medical University; Patrick Wen, MD, Dana-Farber Cancer Institute [DFCI])

Timothy Cloughesy from UCLA and Patrick Wen presented an overview of the development of current response criteria and their strengths and weaknesses. Additional details are summarized in the review of this section later in this supplement (Panel 3 paper in this supplement by Reardon et al.).

Overall survival is generally considered the gold standard for determining whether a cancer treatment is effective, but OS may not directly reflect the impact of a specific regimen because of potential confounding effects of salvage therapies, prognostic factors, and other issues. Objective response rate and PFS are potentially valuable endpoints for isolating the relative benefit of a given therapy.²² At present, the determination of response and progression using surrogate measures of tumor burden often suffer from issues associated with imaging characteristics (enhancement), measurement variability, false positives, and discordance in radiographic interpretation between observers.²³ Therefore, there is a need to refine response assessment in neuro-oncology with the objective of minimizing intrinsic errors and enhancing the accuracy of predicting true response to a particular therapy (Panel 1 paper in this supplement by Ellingson, Van den Bent, Wen and Cloughesy).

In 1990, Macdonald et al²⁰ published criteria for response assessment in HGG (Table 2). These criteria provided an objective radiologic assessment of tumor response and were based on contrast-enhanced CT or MRI scans and the 2D World Health Organization (WHO) oncology response criteria using enhancing tumor area (the product of the maximal cross-sectional enhancing diameters) as the primary tumor measure.^{24,25} These criteria, for the first time, also considered the use of corticosteroids and changes in the neurologic status of the patient. These “Macdonald criteria” enabled comparison of response rates between clinical trials in HGG and were widely adopted in these clinical trials.

Response assessment in most solid tumors is based on 1-dimensional assessment of tumor size using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, introduced in 2000²⁶ and updated in 2009 (RECIST version 1.1).²⁷ Several studies have compared the RECIST criteria with 2D and 3D measurements and volumetric measurements in HGGs^{28–30} and have shown fairly good concordance among the different methods in determining response in adult patients with HGG,^{29,30} as well as in pediatric brain tumors.²⁸ However, the RECIST criteria have not been widely adopted in neuro-oncology because of persistent concerns about using 1D measurements in irregularly shaped tumors, frequently complicated by the presence of a surgical cavity.

While an important advance, the Macdonald criteria had several important limitations.^{31–33} These include the difficulty of measuring irregularly shaped tumors, interobserver variability, the lack of assessment of the nonenhancing component of the tumor, lack of guidance for the assessment of multifocal tumors, and the difficulty in measuring enhancing lesions in the wall of cystic or surgical cavities.¹⁵ In addition, there are significant limitations in equating changes in the enhancing area with changes in tumor size or tumor growth. Enhancement can be decreased by corticosteroids and anti-angiogenic agents that reduce vascular permeability^{15,34,35} and can be increased by a variety of non-tumoral processes, such as treatment-related inflammation, seizures, postsurgical changes, ischemia, infections, subacute radiation effects such as pseudoprogression,³⁶ and radiation necrosis.^{37–41} The limitations of the Macdonald criteria led the RANO Working Group to propose updated response criteria for HGG in 2010.¹⁵ These criteria were built on the Macdonald criteria but included measurement of nonenhancing tumor progression, definitions for measurable and nonmeasurable disease, definition of progression for patients being considered for enrollment into clinical trials, recommendations to address pseudoprogression and pseudoresponse, requirement of confirmatory scans for response, and recommendations for dealing with equivocal imaging changes that allow patients to stay on study with a repeat scan in 4 weeks.¹⁵ See Table 2 for a summary of the different response criteria.

Following standard radiochemotherapy, 20%–40% of patients demonstrated increased enhancement on their first postradiotherapy MRI.³⁶ In 50% of these patients, the increased enhancement

Table 2. Summary of current response criteria

	RECIST	Macdonald	RANO
Measurement	1D contrast enhancement	2D contrast enhancement	2D contrast enhancement + T2/FLAIR
Progression	≥20% increase in sum of lesions	≥25% increase in product of perpendicular diameter	≥25% increase in product of perpendicular diameter
Response	≥30% decrease in sum of lesions	≥50% decrease in product of perpendicular diameter	≥50% decrease in product of perpendicular diameter
Durability of response	Optional	Yes (at least 4 wk)	Yes (at least 4 wk)
Definition of measurability	Yes	No	Yes
Number of target lesions	Up to 5	None specified	Up to 5
T2/FLAIR	Not evaluated	Not evaluated	Evaluated
Corticosteroids considered	No	Yes	Yes
Clinical status considered	No	Yes	Yes
Pseudoprogression considered	No	No	Yes

was a transient effect of radiotherapy termed “pseudoprogression,” which stabilizes or resolves with time. A meta-analysis of pseudoprogression studies suggests that it occurs at a rate of approximately 23% at 1 month after completion of radiotherapy, 19% at 2 months, and 5% at 6 months (Panel 1 paper in this supplement by Ellingson, Van den bent, Wen and Cloughesy). It was felt that the RANO criteria recommendation to exclude patients who progress within 3 months of completion of radiotherapy from recurrent HGG clinical trials was reasonable, since this would exclude the majority of patients with pseudoprogression.¹⁵

With the introduction of bevacizumab and other drugs that affect vascular permeability, up to 40% of patients progress initially with nonenhancing disease, and in approximately 20% of patients this progression is rapid.⁴² The RANO criteria introduced the concept that nonenhancing tumor progression on T2/FLAIR images should also be considered in determining tumor progression.¹⁵ The RANO criteria defines progression as a 25% increase in the sum of the perpendicular diameters of enhancing lesion and includes a significant increase in T2/FLAIR on stable or increasing steroid dose. Although guidance was given on the type of T2/FLAIR changes that may be considered as progressive disease, it was felt that objective measurement of nonenhancing tumor progression was not possible given the limitations of current technology, and determination of nonenhancing progression was left to the investigators’ discretion. This lack of a reliable, quantitative measurement of nonenhancing tumor progression is one of the major limitations of the RANO criteria, and led to debate on whether the inclusion of nonenhancing tumor progression adds additional value to contrast-enhancing progression alone. In a recent study by Huang et al⁴³ comparing the RANO criteria with the Macdonald criteria, the inclusion of T2/FLAIR assessment in the RANO criteria resulted in moderate and statistically significant reduction in median PFS and ORR. In addition, ORR and PFS determined by RANO correlated with OS.⁴³

Despite the limitations of current response criteria, Panel 1 felt that they adequately reflected changes in tumor burden and could be reliably used to determine response. For trials in recurrent HGG treated with agents that do not affect vascular permeability, the response rate is generally less than 5%, and never more than 9% (Table 3), suggesting that therapies that produce responses significantly in excess of these thresholds may have real activity. For agents that affect vascular permeability, such as bevacizumab, the response rates are significantly higher and the thresholds for determining whether an agent is active will also need to be higher (Table 4).

Panel 1 summary

- The current RANO criteria are adequate for determining response in HGG with some limitations. In particular, they are adequate to measure response in single-arm phase II trials, especially for agents that do not affect vascular permeability.
- In recurrent HGG, changes in contrast enhancement generally follow changes in tumor burden. The exceptions include:
 - **Alteration of corticosteroid dose:** can be mitigated by requiring stable dosage for baseline scan and limiting objective response determination if steroid dose is increased (RANO criteria)
 - **Pseudoprogression:** can be mitigated by limiting enrollment of patients into recurrent disease studies who have progressive lesions 12 weeks or later following radiotherapy (RANO criteria)
 - **Single scan showing response may not be reliable:** can be mitigated by confirming response with a second scan after at least 4 weeks and evaluating durability of response (RANO criteria)
 - **Use of agents with direct effects on vascular permeability (eg, anti-VEGF therapies):** can be mitigated by evaluation of nonenhancing tumor (RANO criteria). ORR threshold for determining success may be different for these agents.
- There is debate regarding the value of evaluating nonenhancing tumors using T2/FLAIR images. While 30%–40% of tumors initially develop nonenhancing tumor after anti-VEGF therapies, most tumors subsequently develop enhancing disease that may be more easily measured. Evaluating nonenhancing tumor is intuitively meaningful, but whether there is added value remains to be defined. Utilizing current technology, non-enhancing tumor is not easily measurable, and reproducibility remains an issue.
- The RANO criteria are a work in progress. Implementation and validation in clinical trials will be important. Future revisions may potentially include T1 subtraction maps, volumetric imaging, advanced MRI techniques such as perfusion and diffusion MRI, amino acid PET, neurocognitive function and health-related quality of life measures, corticosteroid use, and neurologic function, if they can be validated.

Panel 1 discussion

- The majority of participants agreed that radiographic response as measured through standard MRI correlates with tumor burden. Participants also determined that the tools to undertake single-arm, phase II trials in some groups of therapies are available now.
 - A single scan showing a response may not be definitive, but this can be supported by confirming response on a follow-up scan and looking for a durability of response.
 - There are challenges in determining tumor response when using current contrast-enhanced techniques, particularly in the context of drugs that affect vascular permeability.
 - When agents affect vascular permeability, there are confounding effects, but evaluating nonenhancing disease could potentially lessen these.
- In recurrent GBM, changes in contrast enhancement generally reflect changes in tumor burden. There are exceptions, and if these are diminished, demonstration of durable objective responses in a single-arm study setting has the potential to represent benefit to patients.
- There is value in measuring the volume of the contrast-enhancing lesion, and this information is relevant to the assessment of tumor burden.
- The current response criteria used in neuro-oncology is the RANO criteria. Application of the RANO criteria is a work in progress, and its validation and shortcomings will be determined by future studies. The RANO criteria may be revised to incorporate newer techniques that might improve quantification, such as contrast enhancement with T1 subtraction maps to better determine response to therapy. Additionally, RANO criteria

Table 3. Summary of recent recurrent GBM studies with drugs that do NOT target VEGF

	Study Name	Year	n Patients	n Recurr	Multicenter?	Central Review?	Time Post XRT	Meas. vs Eval.	ORR	Durability	PFS	PFS-6	OS	Criteria for Response
Non-VEGF Drug Studies														
Batchelor, 2013 ⁴⁴	CCNU	2008–09	65	1	Yes	Yes	12 wk	E	8.9		2.7	25	9.8	Macdonald
Wickl, 2010 ⁴⁵	Enzastaurin	2006–07	174	1–2	Yes	Yes	12 wk	M	2.9		1.5	11	6.6	Levin
Wickl, 2010 ⁴⁵	CCNU	2006–07	92	1–2	Yes	Yes	12 wk		4.3		1.6	19	7.1	Levin
Yung, 2000 ⁴⁶	TMZ		112	1	Yes				5.4			21	7.5	Macdonald
Yung, 2000 ⁴⁶	PCB		113	1	Yes				5.3			8	6	Macdonald
Ballman, 2007 ⁴⁷	NCCTG		345		Yes				NA		1.8	9	5	
Lamborn, 2008 ²²	NABTC		437	1–3	Yes	No	4 wk	M	7		1.9	16	7	Macdonald
Lamborn, 2008 ²²	NABTC TMZ		146	1–3	Yes		4 wk	M	NA		3.5	28	9.3	Macdonald
Lamborn, 2008 ²²	NABTC No TMZ		291	1–3	Yes		4 wk	M	NA		1.6	9	6.1	Macdonald
Yung, 2009 ⁸	TMZ (AG)		162	1	Yes	Yes		M	35		5.4	46	13.6	Macdonald

Abbreviations: XRT, external beam radiation; PFS-6, 6-mo PFS; CCNU, lomustine; TMZ, temozolomide; PCB, procarbazine; NCCTG, North Central Cancer Treatment Group; NABTC, North American Brain Tumor Consortium; AG, anaplastic glioma.

may specify unique response criteria for different treatment types.

- Under circumstances where it is unclear whether images represent progression, it is important to continue to allow the patient to remain on study, as allowed by the RANO criteria, and collect additional imaging data.
- Variability in imaging acquisition and interpretation needs to be reduced, and standardization is critical.
- The FDA is open to having discussions about data before companies commit to a go/no-go decision with regard to different therapies they are developing.

Emerging Techniques and Technologies in Brain Tumor Imaging (Panel 2)

(Martin Bendszus, MD, Heidelberg University Hospital; Benjamin Ellingson, PhD, UCLA; Christian Graff, PhD, FDA; Lou Marzella, MD, PhD, FDA; Whitney Pope, MD, PhD, UCLA; A. Gregory Sorensen, MD, Siemens)

The goal of Panel 2 was to describe the state of imaging techniques and technologies for detecting response of brain tumors to therapies in the setting of multicenter clinical trials. These included techniques such as volumetric MRI and T1 subtraction maps that can potentially be implemented in the near future to improve tumor visualization and quantification, as well as newer technologies such as perfusion and diffusion MRI and amino acid PET, which require additional validation over a longer term before they can be widely adopted.

Standardization of image acquisition

Dr Benjamin Ellingson from UCLA discussed the need for standardization of image acquisition to reduce variability in measurements. Currently, in multicenter studies the heterogeneity of MR scanners

and image acquisition parameters such as field strength, gradient system, manufacturer, sequences, and contrast agent dose and timing, among others, may result in significant changes in tumor measurements or image contrast, potentially more than the changes caused by the therapy under evaluation. To achieve better reproducibility, it will be important to use constant field strength, sequence parameters, contrast agent dose, and contrast agent timing, as well as the same scanner throughout evaluation.

In addition, there is difficulty in defining the exact margins and identifying the largest diameter or perpendicular diameter⁵² leading to high interobserver variability in 1D and 2D tumor measurements.^{23,29,53} Volumetric measurements with automatic or semiautomatic segmentation may potentially reduce interobserver variability.^{54,55}

Contrast-enhanced T1 subtraction MRI

Dr Ellingson provided an overview of contrast-enhanced T1-weighted subtraction (CE-ΔT1w) MRI as a potential technique that could be implemented relatively quickly to improve visualization and quantification of enhancing tumor. This technique involves digital subtraction of postcontrast MRIs from precontrast MRIs to generate (CE-ΔT1w) maps that may provide a more accurate record of tumor extent compared with unsubtracted postcontrast MRIs. In a recent study evaluating contrast-enhancing tumor volumes in patients treated with bevacizumab in the BRAIN trial,⁹ T1 subtraction maps appeared to improve visualization and quantification of tumor volumes and aided better prediction of patient survival compared with conventional segmentation of contrast-enhanced T1-weighted images.⁵⁶

T2/fluid attenuated inversion recovery

Dr Whitney Pope from UCLA discussed the measurement of T2/FLAIR. This technique is sensitive to nonenhancing tumor, gliosis,

Table 4. Summary of recent recurrent GBM studies with drugs that target VEGF

Study Name	Year	n	Patients	n Recurr	Multicenter?	Central Review?	Time Post XRT	Meas. Vs. Eval.	ORR	Durability	PFS	PFS-6	OS	Criteria for Response
VEGF Drug Studies														
Friedman, 2009 ⁹	2006–07	85	1–2	Yes	Yes	Yes	8 wk	M	28.2	5.6	4.2	42.6	9.2	Modified Macdonald
BRAIN Bev														
Friedman, 2009 ⁹	2006–07	82	1–2	Yes	Yes	Yes	8 wk	M	25.9	4.2	5.6	36	9.3	WHO
BRAIN Bev only (FDA)														
BRAIN Bev/CPT-11	2006–07	82	1–2	Yes	Yes	Yes	8 wk	M	37.8	4.3	5.6	50.3	8.7	Modified Macdonald
Gilbert, 2009 ⁴⁸	2007	60		Yes			6 wk		21			39.3		Macdonald
RTOG-0625 Bev/TMZ														
Gilbert, 2009 ⁴⁸	2007	57		Yes			6 wk		28			38.6		Macdonald
RTOG-0625 Bev/CPT11														
Boxerman, 2013 ⁵⁵	2007	107											9	
RTOG-0625														
Kreisl, 2009 ¹⁰	2006–07	48	1+	No	No	No			35		3.7	24%	7.2	Macdonald
NIH									19.6	3.9				WHO
NIH (FDA)	2006–07	56	1+	No	No	Yes			15.2		3.7–	22.3–	7.7 to	RANO
XL-184		151	1–2	Yes	Yes	Yes					4.7	41.7	10.2	
Batchelor, 2013 ⁴⁴	2008–09	131	1	Yes	Yes	Yes	12 wk	E	15.3		3.1	16.2	8	Macdonald
Cedirinib														
de Groot, 2011 ⁵⁰	2007–08	42	1	Yes	Yes	Yes		M	18		2.8	7.7	9.1	Modified
VEGF trap														Macdonald
Iwamoto, 2010 ⁵¹	2007–08	35	1–3	Yes				M&E	5.9		2.8	3	8.2	Macdonald
Pazopanib														

and edema but is not specific. T2/FLAIR quantification is difficult but feasible⁵⁷ and may be relevant in response assessment in anti-angiogenic therapies.⁵⁸ There are no reliable data for determining the value and reliability of T2/FLAIR in a multicenter setting, and integration of T2/FLAIR into response assessment is a focus of current debate.

“Emerging” techniques that require more validation

Dr Pope provided an overview of techniques that require further validation, including DWI and perfusion MRI, while Martin Bendzsus, MD, from the University of Heidelberg discussed amino acid PET.

DWI is sensitive to microscopic motion of water molecules and correlated with tumor cell density. Tightly packed tumor cells have restricted extracellular water motion and a low apparent diffusion coefficient (ADC), while edema and necrosis have lower cell densities and higher ADC values.⁵⁹ There is evidence that it is an early biomarker for cytotoxic therapies, and increases in ADC are associated with a favorable response.⁶⁰ However, variability in acquisition and low reproducibility limit its use in multicenter trials currently.

Perfusion DSC MRI is a technique using a first-pass bolus imaging method to estimate relative cerebral blood volume, relative cerebral blood flow, and mean transit time. Perfusion DSC MRI may improve clinical decision making, increasing the confidence of calling progression⁶¹ and differentiating progression from pseudoprogression.⁶² However, there remains significant inter- and intraobserver variability in perfusion and DCE MRI, limiting their use in multicenter trials.

Amino acid PET is based on the fact that amino acid transport is increased in malignant cells due to increased demand from proliferation, transamination, and transmethylation and use of amino acids for fuel. Amino acid tracers that have shown increased uptake into brain tumors include ¹¹C-methyl-methionine (¹¹C-MET), ¹¹C-tyrosine (¹¹C-Tyr), ¹⁸F-fluoroethyl-L-tyrosine (¹⁸F-FET), and 3,4-dihydroxy-6-[¹⁸F]-fluoro-L-phenylalanine (¹⁸F-DOPA).^{63,64} However, there is little or no multicenter data and information regarding variability. In addition, inflammation causes elevation of neutral amino acid uptake, and it can be difficult to detect active tumor from background tissue.

Future techniques on the horizon

Dr Bendzsus discussed 2 techniques that may eventually help with tumor quantification. Intracellular sodium concentration is elevated in brain tumors and correlates with proliferation rate. Sodium-23 (²³Na) MRI is able to reflect changes in tissue sodium concentrations, although clinical use of this technique is currently limited by low resolution and low signal-to-noise ratio.⁶⁵ Chemical exchange saturation transfer MRI is a potential imaging biomarker for proteins, peptides, amino acids, or pH⁶⁶ and could potentially differentiate tumor from edema.

Panel 2 summary of discussion and recommendations

- The general consensus was that current technology is able to measure the impact of a therapy, especially when the effect is large.

- There is unnecessary variability in the imaging of brain tumors. Four categories of imaging variability were identified, involving acquisition, processing, reading, and patient-related. There was a recommendation to standardize future protocols across multicenter trials, employ a central imaging review panel, and use automated/semiautomated segmentation and volumetric analysis. Other aspects of standardization include use of constant field strengths, sequence parameters, contrast agent dose, and contrast agent timing. At the very least, the same scanner with the same protocol should be used for the same patient over time. The Alzheimer's Disease Neuroimaging Initiative offers a potential model for the neuro-oncology community as they pursue imaging standardization and validation.
- A potential path toward improvement of assessment of brain tumor imaging is the use of CE- Δ T1w maps, if this approach is validated in future studies. Subtraction maps may reduce the error in identifying areas of contrast enhancement. Pre- and postcontrast T1-weighted MRI sequences should be matched and standardized in future multicenter trials to allow appropriate collection of data.
- The added value of T2/FLAIR imaging is an area requiring further investigation. Interpreting T2/FLAIR images can be difficult because the signal is not specific and may arise from gliosis, edema, or tumor. Correlating T2/FLAIR imaging with diffusion MRI may provide a means to differentiate the presence of tumor from other causes of increased T2/FLAIR, since areas of tumor often have low ADC.
- Although promising, diffusion MRI, perfusion MRI (specifically DSC), and amino acid PET require further investigation and validation in multicenter trials to confirm their utility. The increased cost and limited availability of these tests will also have to be taken into account.

Trial Design and Its Impact on Imaging Measurement of Tumor Progression and Tumor Response to Drug (Panel 3)

(Karla Ballman, PhD, Mayo Clinic; Peter Bross, MD, FDA; Jan Buckner, MD, Mayo Clinic; Susan Chang, MD, University of California, San Francisco [UCSF]; Suzanne Demko, PA-C, FDA; Lou Marzella, MD, PhD, FDA; David Reardon, MD, DFCI)

The background paper for Panel 3 related to trial design, and its relationship to imaging measurement of tumor progression and response is included later in this supplement (Panel 3 paper in this supplement by Reardon et al). Dr David Reardon from DFCI provided an overview of clinical trial endpoints in neuro-oncology (Table 5). The typical primary endpoints are OS, ORR, and PFS. Commonly used secondary or exploratory endpoints include net clinical benefits such as quality of life/symptom burden, neurocognitive function, performance status, and corticosteroid requirement, as well as toxicity, pharmacokinetics, imaging, and pharmacodynamic variables. Strengths and limitations/weaknesses of ORR and PFS were discussed and are listed in Tables 6 and 7, respectively.

Factors supporting further drug development for recurrent GBM in a single-arm study were felt to include: (i) standardized imaging acquisition across sites and patients, (ii) response assessment using RANO, (iii) no anticipated effect of drug on vascular

Table 5. Clinical trials endpoints in neuro-oncology

Typical Primary Endpoints	Typical Secondary/Exploratory Endpoints
Overall survival	Net clinical benefit**
Progression-free survival	– Quality of life/symptom burden
Overall radiographic response	– Neurocognitive function
	– Performance status
	– Corticosteroid requirement
	Toxicity
	Pharmacokinetics
	Imaging
	Pharmacodynamic variables

**In development: Objective assessment of neurologic integrity/function (Neurologic Assessment in Neuro-Oncology [NANO] criteria).

Table 6. Strengths and limitations of radiologic response

Strengths	Limitations
(1) Surrogate of clinical benefit: decreased tumor burden = improved symptoms and OS	(1) Dependent on validated assessment method
(2) Appropriate for single-arm design	(2) Unreliable if treatment impacts measurement of tumor burden (anti-VEGF Rx)
(3) Rapid, small, less expensive studies	(3) Thresholds for response: arbitrary
(4) Avoids crossover effect	(4) Does not address durability
(5) Reliable/established benchmarks—recurrent patients prior to Avastin	(5) Nonenhancing lesions?
	(6) Does not “credit” stable disease
	(7) Challenge of geometrically complex lesions
	(8) Interobserver variability
	(9) Independent review beneficial
	(10) Assessment of slow-growing lesions

Factors that can affect enhancing (and nonenhancing tumor):

- Anti-angiogenic agents	- Postsurgical changes
- Corticosteroids	- Ischemia
- Imaging techniques/variables	- Infection
- Inflammation	- Radiation necrosis
- Seizures	- Pseudoprogression

permeability, (iv) significant durability of response, (v) high rate of tumor shrinkage, (vi) central review, (vii) reproducibility between sites/investigators, (viii) association with measure(s) of clinical benefit including a validated PRO for health-related quality of life, neurocognitive function and potential neurologic assessment (Neurologic Assessment in Neuro-Oncology [NANO] criteria), and (ix) association with OS.

Panel 3 summary

Objective response rate is an appropriate endpoint for single-arm trials for antineoplastic agents that do not directly modulate

Table 7. Strengths and limitations of PFS

Strengths	Limitations
Meaningful for HGG	Critically dependent on accurate definition/measure of progression
Not impacted by crossover	Unreliable if therapy impacts measurement of tumor
Credits stable disease	Evaluation time bias
Reliable historic benchmarks	Optimally requires randomized control design
Relatively rapid endpoint	

vascular permeability. The rate of ORR as assessed by currently available imaging techniques is appropriate for single-arm phase II studies among recurrent GBM patients and can potentially support accelerated drug development of promising new agents. For agents that do not increase vascular permeability, the historical benchmarks provide well-established and consistent comparator data to support the evaluation of promising therapies. The duration of radiographic response is an important indicator of meaningful antitumor effect and associated clinical benefit and should also be taken into consideration. Other factors that may add value to a durable ORR rate include: (i) increased rates of overall tumor shrinkage among study participants as reflected by waterfall or spider plots, (ii) reproducibility across studies and investigators, (iii) confirmation by an independent review panel of expert neuroradiologists, (iv) correlation with OS, and (v) correlation with additional measures of clinical benefit (Panel 3 paper in this supplement by Reardon et al).

Panel 3 discussion

- Several panelists stated that in order to be able to use radiographic response as an endpoint in a single-arm study to justify accelerated approval of a therapy, there would need to be substantial, durable, and reproducible objective responses with demonstrable clinically meaningful benefit to the patient. It would be necessary to confirm the findings in a randomized study with survival as an endpoint.
- In the short term, single-arm clinical studies with imaging endpoints may be used as a means to obtain an early signal of efficacy to drive development decisions and possibly for accelerated approval.
- To achieve consensus on the validation and definition of a reasonable threshold for defining radiographic response with varying types of therapeutic interventions, the panel proposed the following priorities for designing clinical trials:
 - Minimize the false positive effects that are not obviously related to the therapy. Use the RANO criteria to help eliminate the proportion of patients with pseudoprogression that go into trials, as well as the effects of corticosteroids on imaging.
 - To give greater confidence that patients are actually deriving benefit from the therapy, it will be necessary to show a relationship between radiographic response and another clinical outcome, such as through evaluation of PROs or through neurocognitive and/or neurologic assessment.

- Use of the most current imaging techniques will require validation. Different measures such as T1-weighted images, T1 subtraction, T2/FLAIR, perfusion imaging, and diffusion imaging should be included in the analysis.
- To ensure accuracy and consistency, imaging thresholds of response and duration of response must be refined and standardized via retrospective and/or prospective analyses:
 - For retrospective analyses, data from properly designed randomized trials are needed.
 - The panel preferred prospective analyses because the acquisition and processing of the images can be standardized from the start. It would also be possible to include additional imaging techniques and modalities with the goal of identifying the most reliable methods for determining tumor shrinkage and duration of response. Data may be sourced from NCI and industry-sponsored trials. This would require an independent organization to hold that data in a way that protects both patients and trial sponsors.
 - In the context of single-arm studies, ORR and duration of response have fewer methodological challenges than endpoints that incorporate time to events. The FDA does not consider time to event analyses of data from single-arm trials interpretable for the purpose of supporting a marketing application.
 - The panel considered validation of methods for imaging assessments of response and progression achievable. However, the path to validation would be greatly facilitated by the existence of better therapies capable of demonstrating more robust antitumor responses.

Creating an Action Plan for Improved Imaging Measured Brain Tumor Endpoints (Panel 4)

(Howard A. Fine, MD, New York University Medical Center; Patricia Keegan, MD, FDA; Rajeshwari Sridhara, PhD, FDA; Michael D. Prados, MD, UCSF; W. K. Alfred Yung, MD, University of Texas MD Anderson Cancer Center).

Panel 4 discussion

- The panel stressed the importance of the need for better treatments and that challenges in imaging interpretation would be diminished by more effective therapies.
- Key areas that were discussed included the importance of obtaining advice from the FDA throughout the process of trial design; collaborating with the neuro-oncology community, industry, and investigators from the start; defining response criteria—especially if imaging is used as a measure of tumor response to the agent; demonstrating that the image of the tumor is sensitive and specific enough to show response to the treatment and ensure its reproducibility; and standardizing imaging acquisition to reduce variability and gain confidence in the measure.
- An important first step is to identify the factors that cause variability and attempt to eliminate or reduce their impact. Standardization of imaging techniques through formulation and adoption of clear guidelines will aid in achieving this goal.

- Response criteria need to be standardized for both single-center and multicenter trials. In addition, acceptable thresholds for defining response need to be confirmed.
- It was agreed that there should be one initial standard, the RANO criteria, which should be used by all stakeholders, but its application and relevance for different classes of therapies will be evaluated going forward.
- The RANO criteria are considered to be reasonably reproducible and accurate. However, two issues should be addressed: (i) applicability across different classes of therapies and (ii) the value of FLAIR (in addition to contrast). The RANO criteria are evolving and will be modified as data from trials are assessed.

Conclusions

The workshop produced a number of suggested action items intended to represent a starting point for future work to improve neuroimaging endpoints in clinical trials:

- (1) Refine and standardize the application of the RANO criteria and evaluate the added benefit of T2/FLAIR progression.
- (2) Understand the modifications to imaging benchmarks of response and progression across therapies with different mechanisms of action.
- (3) Attain consensus from key stakeholders on imaging acquisition standards and criteria for assessing tumor response and progression that can be widely implemented in HGG clinical trials to reduce variability.
- (4) Constantly monitor what we can learn along this trajectory and provide feedback to industry and academic investigators to encourage and facilitate effective drug development.

There was consensus that the RANO criteria should continue to serve as the standard response criteria in brain tumor clinical trials. However, the imaging elements of RANO would benefit from additional clarification, including a clearer definition of response tailored to the type of therapy under investigation and modifications to improve visualization of T1 contrast changes and evaluation of T2/FLAIR. There was also a consensus on the need for standardization of image acquisition and analysis within brain tumor clinical trials. The Jumpstarting Brain Tumor Drug Development Coalition will continue to work with the neuro-oncology and neuroimaging community, the FDA, NCI, and industry to standardize image acquisition and improve imaging response criteria with the goal of accelerating the development of novel therapies for brain tumors.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (<http://neuro-oncology.oxfordjournals.org/>).

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