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RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults

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ABSTRACT

PURPOSE The Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas (RANO-HGG) and low-grade gliomas (RANO-LGG) were developed to improve reliability of response assessment in glioma trials. Over time, some limitations of these criteria were identified, and challenges emerged regarding integrating features of the modified RANO (mRANO) or the immunotherapy RANO (iRANO) criteria.

METHODS Informed by data from studies evaluating the different criteria, updates to the RANO criteria are proposed (RANO 2.0).

RESULTS We recommend a standard set of criteria for both high- and low-grade gliomas, to be used for all trials regardless of the treatment modalities being evaluated. In the newly diagnosed setting, the postradiotherapy magnetic resonance imaging (MRI), rather than the postsurgical MRI, will be used as the baseline for comparison with subsequent scans. Since the incidence of pseudoprogression is high in the 12 weeks after radiotherapy, continuation of treatment and confirmation of progression during this period with a repeat MRI, or histopathologic evidence of unequivocal recurrent tumor, are required to define tumor progression. However, confirmation scans are not mandatory after this period nor for the evaluation of treatment for recurrent tumors. For treatments with a high likelihood of pseudoprogression, mandatory confirmation of progression with a repeat MRI is highly recommended. The primary measurement remains the maximum cross-sectional area of tumor (two-dimensional) but volumetric measurements are an option. For IDH wild-type glioblastoma, the nonenhancing disease will no longer be evaluated except when assessing response to antiangiogenic agents. In IDH-mutated tumors with a significant nonenhancing component, clinical trials may require evaluating both the enhancing and nonenhancing tumor components for response assessment.

CONCLUSION The revised RANO 2.0 criteria refine response assessment in gliomas.

ACCOMPANYING CONTENT

Data Supplement

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BACKGROUND

Gliomas are the most common type of malignant primary brain tumor.[1] Despite extensive research, progress in developing effective therapies has been unacceptably slow.[2-4] The Response Assessment in Neuro-Oncology (RANO) Working Group published response criteria for high-grade gliomas (RANO-HGG) in 2010,[5] and low-grade gliomas (RANO-LGG) in 2011,[6] on the basis of consensus recommendations to improve the reliability and comparability of response assessments across clinical trials and to help identify more effective therapies. These criteria have been widely accepted and incorporated into most glioma clinical trials over the past decade. Over time, concerns regarding challenges of differentiating pseudoprogression secondary to radiochemotherapy and immunotherapies from true disease progression have led to the introduction of modifications of these criteria, including the Modified RANO Criteria (mRANO)[7] and the Immunotherapy RANO Criteria (iRANO),[8] to potentially address these issues. The original RANO-HGG

CONTEXT

Key Objective

Response Assessment in Neuro-Oncology (RANO) 2.0 is an update of the response criteria for gliomas in adults on the basis of data from evaluation of the original RANO criteria and variations such as the modified RANO criteria (mRANO) and the immunotherapy RANO criteria (iRANO).

Knowledge Generated

RANO 2.0 recommends a standard set of criteria for both high- and low-grade gliomas, to be used for all trials regardless of the treatment modalities being evaluated. Response criteria for contrast-enhancing tumors, non–contrast-enhancing tumors, and tumors with both enhancing and nonenhancing components are proposed, in addition to other guidance to improve the assessment of response and progression in glial tumors.

Relevance *(J.P.S. Knisely)*

RANO 2.0 provides unified, standardized guidelines for glioma response assessments that are applicable for all low- and high-grade tumors. Subclassifications for enhancing or nonenhancing tumors or for the type of antitumor therapy employed are no longer needed.*

*Relevance section written by *JCO* Associate Editor Jonathan P.S. Knisely, MD.

criteria anticipated these challenges and included language recommending that if there is uncertainty regarding progression, the patient may continue treatment and undergo repeat imaging to confirm progression before necessitating coming off study. The mRANO criteria differs from RANO-HGG in using the first postradiotherapy magnetic resonance imaging (MRI) instead of the postsurgical MRI as the baseline, and mandates a repeat MRI to confirm progression.[7] The iRANO criteria use the postoperative MRI as the baseline, similar to RANO-HGG. However, within the first 6 months of initiating an immunotherapy, repeat scans over a 3-month period are recommended to confirm disease progression before patients are taken off study.[8] RANO-HGG, mRANO, and iRANO have been used in different clinical trials, leading to variability in response assessments and uncertainty about which set of criteria to use. There is a need for updated response criteria for glioma trials based upon clinical validation of the various criteria.

Previous response criteria for gliomas have been based primarily on expert recommendations. The RANO working group felt it was important to update the response criteria informed by available data. The following recommendations for RANO 2.0 have been guided in part by the results of a study comparing RANO-HGG, mRANO, and iRANO in 526 patients with newly diagnosed glioblastoma and 580 patients with recurrent glioblastoma treated with both conventional therapies and on clinical trials (see Data Supplement, Supplement and Fig S1 for summary [online only]).[9] This study found no difference in progression-free survival (PFS), PFS at 6 months (PFS6), or in the Spearman correlation between PFS and survival between RANO-HGG, mRANO, and iRANO in either newly diagnosed or recurrent glioblastoma. Using a repeat scan to confirm progression appeared to be helpful in the first 3 months after radiotherapy, given the poor correlation between progression and survival during this period but the use of confirmation scans at any other time point, regardless of the treatment modality, was not helpful. Measuring nonenhancing progression also did not increase the correlation to overall survival, even in patients receiving bevacizumab.[9] These data support findings from other studies that also questioned the value of assessing nonenhancing progression in patients with glioblastoma.[7,10,11]

In 2021, the WHO published a revised classification of CNS tumors.[12-14] As a result, the traditional distinction of high-grade gliomas as enhancing tumors evaluated by RANO-HGG, and low-grade gliomas as nonenhancing tumors evaluated by RANO-LGG, has become less clear. For example, *IDH* wild-type astrocytoma with molecular features of glioblastomas may be nonenhancing, while enhancement can occur in high-grade *IDH*-mutated gliomas. Given this revised pathologic classification, the RANO Working Group felt that instead of separate RANO-HGG and RANO-LGG criteria, a single unified set of response criteria for all gliomas would be more appropriate.

The following sections outline recommendations for updated response criteria from the RANO Working Group, RANO 2.0 intended to be used for glioblastomas, all grades of *IDH*-mutated gliomas, and other glial tumors, regardless of the specific therapies being evaluated (see the Data Supplement [Supplement] for process of developing RANO 2.0).

METHOD OF MEASUREMENT

Contrast-enhanced MRI is the most sensitive and reproducible method of assessment of brain tumors.[15] The same imaging protocol should be used to characterize each identified and reported lesion at baseline and across all

subsequent imaging time points to ensure that the assessment of interval appearance or disappearance of lesions, or changes in size are not affected by scan parameters such as slice thickness. The standardized brain tumor imaging protocol (BTIP) should be used to reduce variability (Data Supplement, Table S1).[16] Importantly, more advanced validated sequences can be added, if necessary, and integrated into the BTIP protocol. Ideally, to reduce variability, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of their study participation.

Two-Dimensional Versus Volumetric Assessment

As with RANO-HGG, the product of the maximal cross-sectional diameters of the enhancing lesions will be used to determine the size of contrast-enhancing lesions. As with RANO-LGG, the maximal cross-sectional T2-weighted fluid-attenuated inversion recovery (FLAIR) diameters will be used to determine the size of non–contrast-enhancing lesions.[5,6]

Despite growing interest in replacing two-dimensional measurements with volumetric analysis to provide more accurate assessment of tumor size, studies to date have not demonstrated a conclusive benefit of volumetric analysis over two-dimensional measurement[17-19] with rare exceptions,[20] and there remain challenges with limitations of the software used for volumetric analysis, their availability, as well as the added costs, complexity, and logistical challenges. Two-dimensional tumor measurement will remain the recommended primary measurement, but volumetric measurements can be used if available. Importantly, for any specific trial, two-dimensional or volumetric measurements should be prespecified for all treated patients to optimize consistency. The proposed cutoff for partial response (PR) will be a 65% reduction in volume to be consistent with the 50% reduction in area with the current criteria, and 40% increase in volume will constitute progression to be consistent with the 25% increase in area (Data Supplement, Table S2).[21]

Definitions

Measurable and Nonmeasurable Disease

Measurable disease is defined as contrast-enhancing or non–contrast-enhancing lesions with clearly defined margins by MRI scan, with both perpendicular diameters on a single slice of at least 10 mm, visible on two or more slices that are preferably, at most, 4 mm apart with 0-mm interslice gap. The plane of lesion measurement in 2D (axial, coronal, or sagittal) should be chosen based on the plane with the largest lesion extent. Volumetrically, measurable disease in 3D will be defined as having contrast-enhancing or nonenhancing disease of at least 1 cm in all three orthogonal directions. Although not recommended, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline for both perpendicular measurements should be two times the slice thickness and interslice gap (eg, if the slice thickness is 5 mm with 1.5-mm interslice gap, the minimum tumor size on both perpendicular dimensions should be 13 mm).[7] Measurement of tumor around a cyst or surgical cavity remains challenging. Such lesions should generally be considered nonmeasurable unless there is a nodular component measuring ≥10 × 10 mm in diameter. The cystic or surgical cavity should not be measured in determining therapeutic response.

Nonmeasurable disease remains defined as either unidimensionally measurable lesions, masses with unclear margins, or lesions with maximal perpendicular diameters <10 mm. Patients without measurable disease, such as those who have undergone a gross total resection, cannot exhibit a response to subsequent treatment and can only achieve stable disease (SD) as their best radiologic outcome, assuming treatment is started before there is radiologic evidence of new tumor growth. Therefore, only patients with measurable disease can be included in the assessment of overall response rate, while patients without measurable disease may be included in assessments for other outcomes such as time-to-event end points (eg, PFS or survival) and clinical functioning.

Algorithms for determining measurable and nonmeasurable disease are included in the Data Supplement (Fig S2).[7]

Target Lesions

When multiple measurable lesions exist, at least two and no more than three lesions should be identified as target lesions for studies evaluating either enhancing or nonenhancing tumors. For studies evaluating both enhancing and nonenhancing tumors, a maximum of two measurable enhancing and two measurable nonenhancing lesions can be identified as target lesions. The enhancing lesion(s) can be in the nonenhancing tumor. The sum of the products of the perpendicular diameters of these lesions should be determined. Generally, the largest enlarging lesion(s) should be selected. Emphasis should also be placed on lesions that allow reproducible repeated measurements. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected. For patients with multiple lesions, those that are increasing in size should be selected as target lesions, regardless of their relative size. The other lesions will be considered nontarget and should be recorded but not integrated into the total lesion size calculation (Data Supplement, Fig S2).

Baseline MRI

The immediate postoperative MRI scan, obtained within 48 hours of surgery, has been used as the baseline MRI in most response criteria for newly diagnosed gliomas, including RANO-HGG[5] and iRANO.[8] By contrast, the mRANO criteria[7] recommend using the first postradiotherapy MRI as the baseline for newly diagnosed gliomas to reduce the impact of the increased contrast enhancement from

TABLE 1. Response Criteria for Enhancing Tumors

CR
CR requires all the following criteria compared with the baseline scan:
(1) Complete disappearance of all enhancing measurable, nonmeasurable, and nontarget disease sustained for at least 4 weeks
(2) No new lesions
(3) Patient must be off corticosteroids or on physiologic replacement doses only
(4) Stable or improved clinically
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable disease only at baseline cannot have CR; the best response possible is SD
PR
PR requires all the following criteria compared with the baseline scan:
(1) ≥50% decrease in the sum of products of perpendicular diameters, or ≥65% decrease in total volume, of all measurable enhancing target lesions sustained for at least 4 weeks
(2) No new lesions
(3) No progression of nonmeasurable enhancing disease[a] or nontarget lesions[b] (see legend below)
(4) Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan
(5) Stable or improved clinically
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable disease only at baseline cannot have PR; the best response possible is SD
SD
SD occurs if the patient does not qualify for CR, PR, or PD (see next section) and requires
(1) Stable area(s) of enhancing target lesions on imaging
(2) No new lesions
(3) No progression of nonmeasurable disease[a] or nontarget lesions[b] (see legend below)
(4) Patients must be on a corticosteroid dose that is not greater than the dose at the time of baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose
(5) Stable or improved clinically
PD
Progression is defined by any of the following compared with baseline or best response after initiation of therapy if there has been a reduction from baseline:
(1) ≥25% increase in sum of the products of perpendicular diameters, or ≥40% increase in total volume of enhancing target lesions, on stable or increasing doses of corticosteroids
If confirmation scans are required (within 12 weeks of completion of radiotherapy and at other time points in studies of agents associated with a high incidence of pseudoprogression), then at least two sequential scans separated by ≥4 weeks both exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions compared with the most recent previous scan will be required. If the second scan at least 4 weeks later exhibits SD or PR/CR, the previous scan showing preliminary PD is noted as pseudoprogression and the patient should continue on therapy (Data Supplement, Fig S3A). The original MRI showing preliminary PD or the second scan, depending on which scan has the smallest sum of the products of the perpendicular diameters or volume, will serve as the baseline for future comparison
(2) Appearance of a new lesion. In the case where the baseline or best response demonstrates no measurable enhancing disease (visible or not visible), then any new measurable (≥10 mm × 10 mm) enhancing lesions are considered PD. If there is uncertainty regarding progression, the patient may continue on treatment and remain under close observation (eg, re-evaluated at 4-week intervals). If subsequent evaluations confirm progression, the date of progression should be backdated to the time point at which this concern for progression was first raised
If confirmation scans are required, any new measurable (≥10 mm × 10 mm) enhancing lesions should not be immediately considered PD, but instead should be added to the sum of bidimensional products or total volume representing the entire enhancing tumor burden. The new lesion will be considered PD if confirmed by a subsequent scan ≥4 weeks later exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the scan first illustrating new measurable disease. If the second scan at least 4 weeks later exhibits SD, CR, PR, or becomes nonmeasurable, the initial scan is noted as pseudoprogression, and the patient should continue on therapy until a second increase in tumor size is observed
(3) Appearance of definite leptomeningeal disease
(4) Clear progression of nonmeasurable lesions (increase in bidirectional diameters by at least 5 × 5 mm to ≥10 × 10 mm[a]; see legend below)
(5) Unequivocal progression of existing nontarget lesions[b] (see legend below)
(6) Definite clinical deterioration not attributable to decrease in corticosteroid dose or other causes apart from the tumor

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TABLE 1. Response Criteria for Enhancing Tumors (continued)

PD
(7) Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression unless caused by documented nonrelated disorders
Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for SD or PD. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having SD; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary

Abbreviations: CR, complete response; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Progression of nonmeasurable lesions requires increase in bidirectional diameters by at least 5 × 5 mm to ≥10 × 10 mm. This should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions and the progressing nonmeasurable lesion(s).
[b]Progression of nontarget lesions requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the lesion(s). This should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions and the progressing nontarget lesion(s). The designation of overall progression based solely on progression in nontarget disease in the face of SD or PR of target disease is uncommon.

pseudoprogression after radiochemotherapy,[22-25] and address the challenges associated with immediate postoperative scans including the presence of postoperative changes (blood products and edema), and variability in corticosteroid dosing, timing of the scans, and imaging techniques used. In support of this approach, Youssef et al[9] showed greater correlation between PFS and OS when the postradiotherapy scan was used as a baseline compared with the postoperative scan, although this difference was not statistically significant. Given these factors, if a patient is sufficiently stable clinically, we recommend using the postradiotherapy MRI scan, performed around 4 weeks (21-35 days) from the end of radiotherapy, as the baseline scan in newly diagnosed gliomas for comparison with future imaging studies. Patients who deteriorate significantly before the postradiotherapy baseline MRI can be taken off study for clinical progression. For patients with newly diagnosed glioma not undergoing radiotherapy, the postsurgery, pretreatment MRI will be used as the baseline. The pretreatment MRI will also be used for patients with recurrent glioma as the baseline. Ideally, baseline scans should be performed as close as possible to the initiation of therapy with an interval not exceeding 14 days, especially for glioblastomas.[26]

Although the immediate postoperative MRI will no longer be used as the baseline for response assessment, this scan still has value in detecting postsurgical complications and determining the extent of resection, which has prognostic implications.[27]

Criteria for Entry on to Clinical Trials for Recurrent/Progressive Disease

We propose that a 25% increase in the sum of the products of perpendicular diameters of the lesions, or a 40% increase in volume, or a new measurable lesion, while on stable or increasing doses of corticosteroids should be required for enrollment onto clinical trials for recurrent disease. Clinical deterioration or increase in corticosteroid dosing alone is not sufficient to indicate progressive disease (PD) for entry into trials.

Given the challenges of determining radiologic progression, we recommend routine collection of all neuroimaging studies for at least 3 months for recurrent glioblastomas and CNS WHO grade 4 *IDH*-mutated astrocytomas, and 12 months for CNS WHO grade 2 and 3 *IDH*-mutated gliomas and other glial tumors, before enrollment to allow for confirmation of progression. Although not mandatory for clinical trial participation, such guidance will help diminish the likelihood of premature or inaccurate progression determination and subsequent inappropriate clinical trial enrollment.

Since the incidence of pseudoprogression is high in the first 12 weeks after chemoradiotherapy for glioblastomas (occurring in up to 30%-40% of patients),[9,25,28,29] and there is poor correlation between radiologic changes and PD and survival during this period,[9] we propose that if a patient with concern for radiologic progression during this period is clinically stable, a repeat MRI should be performed (eg, at 4- or 8-week intervals) to confirm progression (additional 25% or more increase in area or 40% increase or more in volume compared with previous scan) before necessitating a patient coming off study. If follow-up imaging supports true tumor progression, the date of progression should be backdated to the time of the scan when progression was first measured. Patients who develop progression in the first 12 weeks after completion of radiotherapy should be excluded from clinical trials for recurrent disease unless the progression is clearly outside the radiation field (eg, beyond the high-dose region or 80% isodose line) or there is pathologic confirmation of disease progression.[30] We recognize the limited reliability of pathology currently in differentiating progression from pseudoprogression,[31,32] and a RANO working group is currently addressing this issue. Advanced imaging techniques such as diffusion MRI, dynamic susceptibility contrast (perfusion) MRI,[33] and

TABLE 2. Criteria for Nonenhancing Disease

CR
CR requires all the following criteria compared with the baseline scan
(1) Complete disappearance of the target lesion(s) on T2 or FLAIR imaging. If enhancement had been present, it must have resolved completely
(2) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement
(3) Disappearance of all nontarget lesions
(4) Patients must be off corticosteroids or only on physiologic replacement doses
(5) Stable or improved clinically
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable nonenhancing disease only at baseline cannot have CR; the best response possible is SD

PR
PR requires all the following criteria compared with the baseline scan
(1) ≥50% decrease in the sum of the products of perpendicular diameters or ≥65% decrease in total volume of the target lesion(s) on T2 or FLAIR imaging, sustained for at least 4 weeks
(2) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement
(3) No progression of nonmeasurable disease[a] or nontarget lesions[b] (see legend below)
(4) Patient must be on a corticosteroid dose that is not greater than the dose at the time of baseline scan
(5) Stable or improved clinically.
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable nonenhancing disease only at baseline cannot have PR; the best response possible is SD

MR: applies only to nonenhancing disease
MR requires all the following criteria compared with baseline
(1) Decrease between 25% and 50% in the sum of the products of perpendicular diameters, or between 40% and 65% of the total volume of the nonenhancing target lesion(s) on T2 or FLAIR MRI compared with baseline, sustained for at least 4 weeks
(2) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement
(3) No progression of nonmeasurable disease or nontarget lesions[b] (see legend below)
(4) Patients should be on a corticosteroid dose that should not be greater than the dose at the time of baseline scan
(5) Stable or improved clinically
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable nonenhancing disease only at baseline cannot have MR; the best response possible is SD

SD
SD occurs if the changes do not qualify for CR, PR, or MR, or PD and requires
(1) Stable area(s) of nonenhancing target lesions on T2 or FLAIR imaging
(2) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement
(3) No progression of nonmeasurable disease[a] or nontarget lesions[b] (see legend below)
(4) Patients should be on a corticosteroid dose that is not greater than the dose at the time of baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose
(5) Stable or improved clinically

PD
Progression is defined by any of the following compared with baseline or best response after initiation of therapy if there has been a reduction from baseline
(1) ≥25% increase in sum of products of perpendicular diameters, or ≥40% increase in total volume, of the T2 or FLAIR nonenhancing target lesion(s) on stable or increasing doses of corticosteroids not attributable to radiation effect, edema, or comorbid events
(2) Appearance of new lesions or contrast enhancement. In the case where the baseline or best response demonstrates no measurable disease (visible or not visible), then any new measurable (>10 mm × 10 mm) nonenhancing or enhancing lesions are considered PD. If there is uncertainty regarding progression, the patient may continue on treatment and remain under close observation (eg, re-evaluated at 4-week intervals). If subsequent evaluations confirm progression, the date of progression should be backdated to the time point at which this concern for progression was first raised
(3) The appearance of definite leptomeningeal disease
(4) Clear progression of nonmeasurable lesions (increase in bidirectional diameters by at least 5 × 5 mm to ≥10 × 10 mm[a]; see legend below)
(4) Unequivocal progression of existing nontarget lesions[b] (see legend below)

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TABLE 2. Criteria for Nonenhancing Disease (continued)

PD
(5) Definite clinical deterioration not attributable to decrease in corticosteroid dose or other causes apart from the tumor
(6) Failure to return for evaluation because of death or deteriorating condition, unless caused by documented nonrelated disorders
Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for SD or PD. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having SD; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; MR, minor response; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Progression of nonmeasurable lesions requires increase in bidirectional diameters by at least 5 × 5 mm to ≥10 × 10 mm. This should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions and the progressing nonmeasurable lesion(s).

[b]Progression of nontarget lesions requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the lesion(s). This should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions and the progressing nontarget lesion(s). The designation of overall progression based solely on progression in nontarget disease in the face of SD or PR of target disease is uncommon.

amino acid positron emission tomography imaging[34] may help differentiate progression from pseudoprogression but require further validation before formal incorporation into RANO 2.0.

For IDH-mutated gliomas and other glial tumors, the time course for pseudoprogression can extend well beyond 3 months.[35] For these tumors, we recommend confirming progression in the first 3 months after completion of radiotherapy and optional confirmation of progression at later time points before entry into trials for recurrent tumors.

Definition of Radiologic Response and Progression

The radiologic response must be determined by comparison to the tumor measurement obtained at the pretreatment baseline or the first postradiotherapy scan for patients with newly diagnosed glioma undergoing radiotherapy. PR is defined as ≥50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable target lesions, or ≥65% reduction in volume, sustained for at least 4 weeks with stable or decreasing corticosteroid doses. PD is defined as ≥25% increase in the sum of products of perpendicular diameters of all measurable target lesions or ≥40% in volume compared with the smallest tumor measurements at either pretreatment baseline or after initiation of therapy. The appearance of a new measurable lesion will also constitute progression unless per-protocol confirmation of progression is required, in which case it should be added to the sum of the existing target lesions, and progression only occurs if there is ≥25% increase in area or ≥40% increase in volume on repeat imaging. The steroid dose must also be considered (Tables 1-3).

Occasionally, unequivocal progression of a nonmeasurable lesion (lesion increasing by at least 5 × 5 mm and becoming measurable [≥10 × 10 mm]) or a nontarget lesion (25% increase in area or 40% increase in volume) may occur. These lesions should be added to the sum of the existing target lesions. These changes would qualify as progression if the total sum of the products of the perpendicular diameters exceeds ≥25% increase in area or ≥40% in volume and require discontinuation of therapy, even in the setting of SD or PR in the target lesions (Tables 1-3).

Contrast-enhancing disease should be measured for *IDH* wild-type glioblastoma, and T2/FLAIR should be measured for *IDH*-mutated nonenhancing gliomas and for the uncommon nonenhancing glioblastomas. For tumors with a mixture of contrast-enhancing and non–contrast-enhancing components, both enhancing and nonenhancing disease can be measured. However, measuring the contrast-enhancing disease only is also acceptable if it is the lesion(s) determining progression for study entry (Tables 1-3).

Tables 1-3 summarize the response criteria. Table 4 summarizes the overall response status. The Data Supplement (Figs S3A-S3D) provides algorithms for determining response. The Data Supplement (Table S3) summarizes the differences between RANO 2.0 and previous response criteria.

Neuroimaging for Confirmation of Progression

For most situations, confirmation of progression as required by mRANO and recommended by iRANO is not necessary to determine progression.[9] The original RANO criteria allow for the optional continuation of treatment and confirmation of progression if radiologic changes are equivocal. In these situations, it is recommended that patients should be observed closely but continue treatment, for example, for another 1-2 treatment cycles. If the subsequent scans confirm progression, the date of progression should be backdated to the time initial tumor progression was noted. Continuation of treatment for equivocal changes may especially be needed for small tumors since measurement errors are magnified. An exception is in the first 12 weeks

TABLE 3. Criteria for Tumors With Both Enhancing and Nonenhancing Components (not related to peritumoral edema)

CR
CR requires all the following criteria compared with the baseline scan
(1) Complete disappearance of all measurable enhancing and nonenhancing target lesion(s) and all nonmeasurable and nontarget lesion(s)
(2) No new enhancing lesions and no new T2 or FLAIR abnormalities apart from those consistent with radiation effects
(3) Patients must be off corticosteroids or only on physiologic replacement doses
(4) Stable or improved clinically
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable disease only at baseline cannot have CR; the best response possible is SD

PR
PR requires all the following criteria compared with the baseline scan
(1) ≥50% decrease in the product of perpendicular diameters or ≥65% decrease in total volume of either the contrast-enhancing target lesion(s) or the T2 or FLAIR target lesion(s), sustained for at least 4 weeks
(2) No new enhancing lesions and no new T2 or FLAIR abnormalities apart from those consistent with radiation effects
(3) No progression of measurable and nonmeasurable disease[a] or nontarget lesions[b] (see legend below)
(4) Patients must be on a corticosteroid dose that is not greater than the dose at the time of baseline scan
(5) Stable or improved clinically
If PR is determined based on reduction in tumor size of enhancing disease, nonenhancing disease must be at least stable and vice versa
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable disease only at baseline cannot have PR; the best response possible is SD

MR: applies only to nonenhancing disease
MR requires all the following criteria compared with baseline
(1) Decrease between 25% and 50% in the sum of the products of perpendicular diameters or between 40% and 65% of the total volume of nonenhancing target lesion(s) on T2 or FLAIR MRI compared with baseline, sustained for at least 4 weeks
(2) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement
(3) No progression of nonmeasurable disease or nontarget lesions[b] (see legend below)
(4) Patients should be on a corticosteroid dose that is not greater than the dose at the time of baseline scan
(5) Stable or improved clinically
MR can only be determined if the enhancing disease is at least stable.
In the absence of a scan confirming durability of response for at least 4 weeks later, this response will be considered only SD. Patients with nonmeasurable disease only at baseline cannot have MR; the best response possible is SD

SD
SD is present if the changes do not qualify for complete, PR, MR, or progression and requires
(1) Stable area(s) of enhancing and nonenhancing target lesions on imaging
(2) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement
(3) No progression of nonmeasurable disease[a] or nontarget lesions[b] (see legend below)
(4) Patients must be on a corticosteroid dose that is not greater than the dose at the time of baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose
(5) Stable or improved clinically

PD
Progression is defined by any of the following compared with baseline or best response after initiation of therapy if there has been a reduction from baseline
(1) ≥25% increase in sum of the products of perpendicular diameters, or ≥40% increase in total volume of enhancing or nonenhancing target lesions, or both, on stable or increasing doses of corticosteroids not attributable to radiation effect, edema, or comorbid events
If confirmation scans are required (within 12 weeks of completion of radiotherapy and at other time points in studies of agents associated with a high incidence of pseudoprogression), then at least two sequential scans separated by ≥4 weeks both exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions compared with the most recent previous scan will be required. If the second scan at least 4 weeks later exhibits SD or PR/CR, the previous scan showing preliminary PD is noted as pseudoprogression and the patient should continue on therapy (Data Supplement, Fig S3). The original MRI showing preliminary PD or the second scan, depending on which scan has the smallest sum of the products of the perpendicular diameters or volume, will serve as the baseline for future comparison

(continued on following page)

TABLE 3. Criteria for Tumors With Both Enhancing and Nonenhancing Components (not related to peritumoral edema) (continued)

PD
(2) Appearance of a new enhancing or nonenhancing lesion. In the case where the baseline or best response demonstrates no measurable disease (visible or not visible), then any new measurable (>10 mm × 10 mm) lesions are considered PD. If there is uncertainty regarding progression, the patient may continue on treatment and remain under close observation (eg, re-evaluated at 4-week interval). If subsequent evaluations confirm progression, the date of progression should be backdated to the time point at which this concern for progression was first raised
If confirmation scans are required, any new measurable (>10 mm × 10 mm) lesions should not be immediately considered PD, but instead should be added to the sum of bidimensional products or total volume representing the entire enhancing tumor burden. The new lesion will be considered PD if confirmed by a subsequent scan ≥4 weeks later exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the scan first illustrating new measurable disease. If the second scan at least 4 weeks later exhibits SD, CR, PR, or becomes nonmeasurable, the initial scan is noted as pseudoprogression, and the patient should continue on therapy until a second increase in tumor size is observed
(3) Appearance of definite leptomeningeal disease
(4) Clear progression of nonmeasurable lesions (increase in bidirectional diameters by at least 5 × 5 mm to ≥10 × 10 mm[a]; see legend below)
(5) Unequivocal progression of existing nontarget lesions[b] (see legend below)
(6) Definite clinical deterioration not attributable to decrease in corticosteroid dose or other causes apart from the tumor
(7) Failure to return for evaluation because of death or deteriorating condition, unless caused by documented nonrelated disorders
Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for SD or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having SD; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; MR, minor response; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Progression of nonmeasurable lesions requires increase in bidirectional diameters by at least 5 × 5 mm to ≥10 × 10 mm. This should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions and the progressing nonmeasurable lesion(s).

[b]Progression of nontarget lesions requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the lesion(s). This should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions and the progressing nontarget lesion(s). The designation of overall progression based solely on progression in nontarget disease in the face of SD or PR of target disease is uncommon.

after completion of radiochemotherapy in *IDH* wild-type glioblastoma, when pseudoprogression is most commonly observed.[28] In this period, if imaging studies show worsening, for clinically stable patients, a repeat MRI should be performed to confirm progression before taking a patient off study (Tables 1 and 3 and Data Supplement, Figs S3A and S3D). We recognize that there may be therapies that are especially likely to be associated with high rates of pseudoprogression or radiation necrosis (eg, intratumoral therapies such as oncolytic viruses). For clinical trials of such agents, mandatory confirmation of progression with follow-up MRI can be considered.

In general, pseudoprogression is largely associated with changes in contrast enhancement. Therefore, confirmation of progression is recommended in selected cases evaluated with the criteria for contrast-enhancing tumors but is unnecessary in assessing nonenhancing tumors.

Evaluation of Nonenhancing Progression in Patients With Glioblastoma

The original RANO-HGG criteria were developed partly to address the challenges posed by therapies that reduce vascular permeability, including bevacizumab. This reduction in vascular permeability can give rise to pseudoresponses and nonenhancing tumor progression.[5] RANO-HGG incorporated a qualitative evaluation of T2/FLAIR changes into the response criteria to address the issue of nonenhancing progression. Specifically, patients on antiangiogenic agents with stable or decreased contrast enhancement with progression of T2/FLAIR abnormality were determined to have progressed.[5] Although up to 40% of patients treated with bevacizumab develop nonenhancing progression,[36] and its evaluation results in shorter PFS,[37] most patients develop enhancing progression within 1-2 months after nonenhancing progression, resulting in no increase in correlation of PFS with survival.[9,10,37] Furthermore, nonenhancing progression is challenging to distinguish from other causes of increased T2/FLAIR signal, including radiation changes, postsurgical changes, edema, or corticosteroid dosing changes. T2/FLAIR signal abnormality is also difficult to measure reliably, contributing to increased workload and cost.[38] Some treatments such as immunotherapies or intratumoral therapies can be associated with increased peritumoral edema and T2/FLAIR changes on MRI independent of tumor progression. Given the limited value of evaluating nonenhancing progression in enhancing glioblastoma, we recommend removing it from the criteria for determining progression from most trials. Evaluation of

TABLE 4. Summary of Overall Response Status

Target Lesion[a] (current scan)	Target Lesion[b] (previous scan)	New Measurable Disease	Nontarget or Nonmeasurable Lesion(s)	Clinical Status	Increased Steroid Use	Steroid Dose	Overall Response Status
CR	Baseline/SD/PR	No	None/stable	Stable/improved	No[c]	None[c]	Preliminary CR
CR	CR	No	None/CR	Stable/improved	No	None	Confirmed CR
CR	Baseline/SD/PR/CR	Yes	None/CR	Stable/improved	No	None	PD[d]
CR	Baseline/SD/PR/CR	No	None/CR	Worse	No	None	PD
CR	Baseline/SD/PR/CR	No	Worse[e]	Stable/improved	No	None	PD[e]
CR	Baseline/SD/PR/CR	No	None/CR	Stable/improved	Yes	Yes	SD or PD[f]
PR	Baseline/SD	No	None/stable	Stable/improved	No[c]	None[c]	Preliminary PR
PR	PR	No	None/stable	Stable/improved	No	None	Confirmed PR
PR	Baseline/SD/PR	Yes	None/stable	Stable/improved	No	None	PD[d]
PR	Baseline/SD/PR	No	None/stable	Worse	No	None	PD
PR	Baseline/SD/PR	No	Worse[e]	Stable/improved	No	None	PD[e]
PR	Baseline/SD/PR	No	None/stable	Stable/improved	Yes	Yes	SD or PD[f]
SD	Baseline/SD	No	None/stable	Stable/improved	No[c]	None[c]	SD
SD	Baseline/SD	Yes	None/stable	Stable/improved	No	None	PD[d]
SD	Baseline/SD	No	None/stable	Worse	No	None	PD
SD	Baseline/SD	No	Worse[e]	Stable/improved	No	None	PD[e]
SD	Baseline/SD	No	None/stable	Stable/improved	Yes	Yes	SD or PD[f]
PD	Baseline/SD/PR/CR	No	None/stable	Stable/improved	No[c]	None[c]	PD or preliminary PD[h]
PD	Preliminary PD[g]	No	None/stable	Stable/improved	No	None	Confirmed PD
PD	Baseline/SD/PR/CR	Yes	None/stable	Stable/improved	No	None	PD[d]
PD	Baseline/SD/PR/CR	No	None/stable	Worse	No	None	PD
PD	Baseline/SD/PR/CR	No	Worse[e]	Stable/improved	No	None	PD[e]
PD	Baseline/SD/PR/CR	No	None/stable	Stable/improved	Yes	Yes	PD

NOTE. For patients who have both enhancing and nonenhancing lesions evaluated, CR and PR for either contrast-enhancing or T2/FLAIR lesions must be accompanied by at least SD in the other lesions. PD in either contrast-enhancing or T2/FLAIR lesions will qualify as progression, regardless of the response in the other lesions.

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; MR, minor response; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Contrast-enhancing or non–contrast-enhancing lesion(s) or both depending on the criteria used.

[b]Contrast-enhancing or non–contrast-enhancing lesion(s) or both depending on the criteria used.

[c]None or physiologic replacement doses.

[d]New sites of measurable disease constitute PD in the case of no measurable disease at baseline or best response. If confirmation scans are required, new sites are added to the sum of bidimensional products or total lesion volume. The new lesion will be considered PD if confirmed by a subsequent scan ≥4 weeks later exhibiting ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in total volume of enhancing lesions relative to the scan first illustrating new measurable disease.

[e]Progression of nonmeasurable lesions occurs when lesions that are not measurable becomes measurable (10 × 10 mm). Nontarget lesions qualify for progression if there is ≥25% increase in area or 40% increase in volume). For both nonmeasurable and nontarget lesions, the increase should be added to the sum of the target lesions. The designation of overall progression requires ≥25% increase in sum of products of perpendicular diameters or ≥40% increase in volume of the target lesions together with the nonmeasurable or nontarget lesion(s).

[f]Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for SD or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having SD; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

[g]Only relevant when confirmation of progression is required.

[h]PD if no confirmation of progression required; preliminary PD if confirmation of progression required. If next scan shows CD/PR/CR, then progression is not confirmed and the previous scan showing preliminary PD is noted as pseudoprogression and the patient continued on therapy. The original MRI showing preliminary PD or the second scan, depending on which scan has the smallest sum of the products of the perpendicular diameters or volume, will serve as the baseline for future comparison.

T2/FLAIR changes remains of value for evaluation of *IDH*-mutated gliomas with a nonenhancing component and in trials evaluating agents anticipated to significantly affect vascular permeability.

Assessment of Clinical Deterioration

Clinical deterioration remains an important component for response assessment, particularly for determining progression. Although the determination of clinical deterioration continues to be left to the treating physician's discretion, it is recommended that a decline in KPS for at least 7 days from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any baseline to 50 or less be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

The Neurologic Assessment in Neuro-Oncology (NANO) scale was developed as a simple, standardized tool providing a quantifiable evaluation of nine relevant neurologic domains to determine neurologic function (Data Supplement, Fig S4).[39] This tool is being used increasingly in clinical trials to assess response but formal incorporation into the RANO criteria will require further validation studies.

Advanced Imaging Techniques

There is increasing evidence that advanced imaging techniques including perfusion imaging (dynamic susceptibility contrast or dynamic contrast-enhanced MRI), diffusion imaging, magnetic resonance spectroscopy, and amino acid positron emission tomography may help predict tumor response or allow the differentiation of pseudoprogression from progression.[33,40-42] There is also increasing interest in the use of automated assessment of response and the use of artificial intelligence.[43,44] Some of these techniques are undergoing validation studies and may eventually be incorporated into the RANO criteria.

In summary, we outline updated response criteria from the RANO Working Group, RANO 2.0. These criteria will be used for all grades of glial tumors regardless of the IDH mutational status or the specific therapies being evaluated. As with the previous criteria, this represents a work in progress and future updates will incorporate novel developments, advanced imaging techniques, and end points as they become validated.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults

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Consulting or Advisory Role: Boehringer Ingelheim, carthera, Genenta Science, Nerviano Medical Sciences, Chimerix, AstraZeneca, Servier, Roche, Incyte, Fore Biotherapeutics
Research Funding: AbbVie (Inst)

Timothy F. Cloughesy
Leadership: Katmai Pharmaceuticals
Stock and Other Ownership Interests: Katmai Pharmaceuticals, Chimerix, Erasca, Inc
Consulting or Advisory Role: Roche/Genentech, Tocagen, VBL Therapeutics, Novartis, Merck, Boehringer Ingelheim, KIYATEC, Bayer, DelMar Pharmaceuticals, QED Therapeutics, Amgen, Katmai Pharmaceuticals, Global Coalition for Adaptive Research, Inovio Pharmaceuticals, Sapience Therapeutics, SonaCare Medical, SERVIER, Lista, Chimerix
Patents, Royalties, Other Intellectual Property: US Provisional Application No.: 62/819,322 Title: Compositions and Methods for Treating Cancer Filing Date: March 15, 2019 Inventor(s): David A. Nathanson et al. FH Reference No.: UCH-17760 (32246-17760) Your Reference No.: (UCLA 2019-630-1) US
Other Relationship: Global Coalition for Adaptive Research, Break Through Cancer

Benjamin M. Ellingson
Consulting or Advisory Role: Siemens, Medicenna, MedQIA, Imaging Endpoints, Neosoma, Kazia Therapeutics, VBL Therapeutics, Global Coalition for Adaptive Research, Servier, Janssen, Chimerix, Sumitomo Dainippon Pharma Oncology, ImmunoGenesis, Ellipses Pharma, Monteris Medical, Alpheus Medical
Research Funding: Siemens, Janssen
Travel, Accommodations, Expenses: Siemens

Michael Weller
Honoraria: Novocure, Bayer, Pierre Fabre
Consulting or Advisory Role: Curevac, Medac, Novartis, Orbus Therapeutics, Philogen, Roche, Sandoz, Janssen, Seagen, LEO Pharma, Bayer
Research Funding: Quercegen Pharmaceuticals (Inst), Versameb (Inst)

Evanthia Galanis
Consulting or Advisory Role: KIYATEC, Karyopharm Therapeutics (Inst), Boston Scientific (Inst), Servier (Inst)
Research Funding: MedImmune (Inst), Servier (Inst), Celgene (Inst), Denovo Biopharma (Inst), Denovo Biopharma (Inst)

Daniel P. Barboriak
Uncompensated Relationships: Blue Earth Diagnosticds

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Employment: Alaunos Therapeutics, Brii Biosciences
Stock and Other Ownership Interests: WuXi Biologics, Alaunos Therapeutics, Brii Biosciences
Consulting or Advisory Role: Merck, Mundipharma Research, Bioasis Technologies, InSightec, Samus Therapeutics, Karyopharm Therapeutics, Cure Brain Cancer Foundation, Sapience Therapeutics, Monteris Medical, Kintara Therapeutics, Kazia Therapeutics, CarThera, Sumitomo Dainippon Pharma Oncology, VBI Vaccines, Chimerix, Aucentra Therapeutics, Midatech Pharma, Servier, Telix Pharmaceuticals, Alpha Pharmaceutical
Research Funding: CarThera (Inst), Haihe Pharmaceutical (Inst), Taiho Pharmaceutical (Inst)
Other Relationship: VBI Vaccines, Chimerix

Raymond Huang
Consulting or Advisory Role: Agios, Nuvation Bio, Nuvation Bio, Vysioneer
Research Funding: Agios, Bristol Myers Squibb

Andrew B. Lassman
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Consulting or Advisory Role: Sapience Therapeutics, Orbus Therapeutics, Novocure, Vivacitas Oncology, Chimerix, Affinia Therapeutics, Neuron-D, Leal Therapeutics, AlphaDetail, AlphaSights, Bluestar Bioadvisors, Clarion Healthcare, ExpertConnect, Gerson Lehrman Group, Guidepoint Global, IP2IPO, KJT, Tavistock Life Sciences, techspert.io, BioClinica, RadMD, Global Coalition for Adaptive Research
Research Funding: AbbVie, Genentech/Roche, Aeterna Zentaris, VBI Vaccines, Pfizer, Karyopharm Therapeutics, Bayer, QED Therapeutics, Orbus Therapeutics, BMS, Chimerix, NextSource, DelMar, Polaris (Inst), Kintara (Inst) Pharmaceuticals, Corden, Kazia Therapeutics, Servier,

Biohaven Pharmaceuticals, Vigeo Therapeutics, Incyte, Abbott Laboratories
Travel, Accommodations, Expenses: AbbVie, Chimerix, Karyopharm Therapeutics, Pfizer, Bridgebio, VBI Vaccines, Helsinn Healthcare, Foundation Medicine, Servier, Anheart Therapeutics

Minesh Mehta
Stock and Other Ownership Interests: Chimerix
Consulting or Advisory Role: Mevion Medical Systems, ZappRx, Xoft, Kazia Therapeutics, Novocure
Patents, Royalties, Other Intellectual Property: WARF patent 14/934,27, Topical Vasoconstritor Preparations and Methods for Protecting Cells During Cancer Chemotherapy and Radiotherapy
Uncompensated Relationships: Xcision Medical Systems

Matthias Preusser
Honoraria: Roche, GlaxoSmithKline, Bayer, Bristol Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, Mundipharma, BMJ Journals, MedMedia, AstraZeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra Pharmaceuticals, Gan & Lee, Servier
Consulting or Advisory Role: Roche, Bristol Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, AbbVie, Bayer, AstraZeneca, Lilly, Daiichi Sankyo/Astra Zeneca, Sanofi, Merck Sharp & Dome, Tocagen, Adastra Pharmaceuticals, Gan & Lee, Servier
Research Funding: Roche (Inst), GlaxoSmithKline (Inst), Boehringer Ingelheim (Inst), Merck Sharp & Dohme, Bristol Myers Squibb (Inst), Daiichi Sankyo (Inst), AbbVie (Inst)
Travel, Accommodations, Expenses: Roche, GlaxoSmithKline, Bristol Myers Squibb, MSD, Mundipharma, Servier

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Consulting or Advisory Role: Beijing Saint Lucia Consulting
Research Funding: Bristol Myers Squibb (Inst), Puma Biotechnology (Inst), Lilly (Inst)

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Stock and Other Ownership Interests: Alpheus Medical, CarThera
Consulting or Advisory Role: Celgene, Northwest Biotherapeutics, Zai Lab, InSightec, Celularity, CranioVation, Triact Therapeutics, Hemispherian, GT Medical Technologies, Novocure, AstraZeneca, Boston Scientific, Carthera, The Lockwood Group, Boston Biomedical, Novartis, AimedBio
Research Funding: CarThera, Bristol Myers Squibb/Celgene (Inst)
Patents, Royalties, Other Intellectual Property: Methods of Determining Responsiveness to Chemotherapeutic Compounds for Cancer Therapy Type: Provisional Serial No. 63/202,761 Filed: June 23, 2021 (Inst)

Javier E. Villanueva-Meyer
Consulting or Advisory Role: GE Healthcare, MedQIA, Alpheus Medical
Research Funding: GE Healthcare

Wolfgang Wick
Consulting or Advisory Role: MSD Oncology (Inst), Roche/Genentech (Inst), SERVIER, GlaxoSmithKline
Research Funding: Roche (Inst), Apogenix (Inst), Pfizer (Inst)

David R. Macdonald
Research Funding: Celgene (Inst), Servier (Inst)

David A. Reardon
Honoraria: Merck, Novocure, Regeneron, Bristol Myers Squibb, Oncorus, Agenus, EMD Serono, Merck KGaA, Taiho Pharmaceutical, Advantagene, Bayer, DelMar Pharmaceuticals, Imvax, Medicenna, Sumitono Dainippon Pharma, Vivacitas Oncology, Anheart Therapeutics, Deciphera, Ellipses Pharma, Genenta Science, Inovio Pharmaceuticals, Kintara Therapeutics, Kintara Therapeutics, KIYATEC, NEUVOGEN, Taiho Pharmaceutical, Y-mAbs Therapeutics
Consulting or Advisory Role: Merck, Novocure, Regeneron, Bristol Myers Squibb, Oncorus, Agenus, EMD Serono, Merck KGaA, Taiho Pharmaceutical, Delmar Pharmaceuticals, Advantagene, Bayer, Imvax, Medicenna, Vivacitas Oncology, Anheart Therapeutics, Ellipses Pharma, Genenta Science, Kintara Therapeutics, Kiyatec, Agios
Research Funding: Celldex (Inst), Incyte (Inst), Agenus (Inst), EMD Serono (Inst), Acerta Pharma (Inst), Omniox, Enterome (Inst)

Michael A. Vogelbaum
Stock and Other Ownership Interests: Infusion Therapeutics
Honoraria: Plus Therapeutics, Chimerix
Consulting or Advisory Role: Olympus, Midatech Pharma
Research Funding: Infusion Therapeutics (Inst), Celgene (Inst), Oncosynergy (Inst), Denovo Biopharma (Inst)
Patents, Royalties, Other Intellectual Property: Patents for drug delivery devices for the brain

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No other potential conflicts of interest were reported.