Title

Immunotherapy response assessment in neuro-oncology: a report of the RANO working group

Journal

The Lancet Oncology, 16(15)

ISSN

1470-2045

Authors

Okada, Hideho

Weller, Michael

Huang, Raymond

et al.

Publication Date

2015-11-01

DOI

10.1016/s1470-2045(15)00088-1

Peer reviewed

Immunotherapy response assessment in neuro-oncology: a report of the RANO working group

Hideho Okada, Michael Weller, Raymond Huang, Gaetano Finocchiaro, Mark R Gilbert, Wolfgang Wick, Benjamin M Ellingson, Naoya Hashimoto, Ian F Pollack, Alba A Brandes, Enrico Franceschi, Christel Herold-Mende, Lakshmi Nayak, Ashok Panigrahy, Whitney B Pope, Robert Prins, John H Sampson, Patrick Y Wen, David A Reardon**

Immunotherapy is a promising area of therapy in patients with neuro-oncological malignancies. However, early-phase studies show unique challenges associated with the assessment of radiological changes in response to immunotherapy reflecting delayed responses or therapy-induced inflammation. Clinical benefit, including long-term survival and tumour regression, can still occur after initial disease progression or after the appearance of new lesions. Refinement of the response assessment criteria for patients with neuro-oncological malignancies undergoing immunotherapy is therefore warranted. Herein, a multinational and multidisciplinary panel of neuro-oncology immunotherapy experts describe immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria based on guidance for the determination of tumour progression outlined by the immune-related response criteria and the RANO working group. Among patients who demonstrate imaging findings meeting RANO criteria for progressive disease within 6 months of initiating immunotherapy, including the development of new lesions, confirmation of radiographic progression on follow-up imaging is recommended provided that the patient is not significantly worse clinically. The proposed criteria also include guidelines for the use of corticosteroids. We review the role of advanced imaging techniques and the role of measurement of clinical benefit endpoints including neurological and immunological functions. The iRANO guidelines put forth in this Review will evolve successively to improve their usefulness as further experience from immunotherapy trials in neuro-oncology accumulate.

Introduction

Immunotherapy for cancer has made exciting progress. The US Food and Drug Administration approved the first vaccine against non-viral cancers (sipuleucel-T)[1] and blocking monoclonal antibodies to the immune checkpoint molecules CTLA-4 (ipilimumab) and PD-1 (pembroluzimab and nivolumab) for metastatic melanoma and non-small-cell lung cancer.[2–5] Chimeric antigen receptor-engineered autologous T cells have induced durable remissions in patients with leukaemia refractory to conventional therapies, including bone marrow transplantation.[6,7] For patients with primary and metastatic neuro-oncological malignancies, clinical trials assessing various immunotherapeutic approaches are underway, and promising preliminary results are emerging.[8–10]

Ongoing evolution of response assessment in neuro-oncology

Traditional imaging response assessment methods, including WHO criteria,[11] Response Evaluation in Solid Tumors (RECIST),[12] and Macdonald criteria,[13] originated in the cytotoxic therapy era when radiographic findings directly represented anti-tumour effect. As oncology treatments have expanded beyond cytotoxic therapy, the effect of therapeutics on tumour imaging findings has become less straightforward. For neuro-oncology, pseudoprogression after radiotherapy and temozolomide chemotherapy,[14] and pseudoresponse after anti-angiogenic drugs,[15] underline challenges with the interpretation of imaging changes in the modern era. The Report Assessment for Neuro-Oncology (RANO) criteria[16] were proposed in 2010 to improve assessment of the evolving complexities of imaging for patients with malignant glioma. Subsequently, variations of the RANO criteria were refined for patients with low-grade glioma[17] and brain metastases.[18]

A key cornerstone of the RANO criteria is guidance for the occurrence of pseudoprogression, which occurs in about 10–20% of newly diagnosed patients with glioblastoma after radiotherapy and temozolomide chemotherapy.[14,19–21] The precise mechanism of pseudoprogression is still poorly understood, but most cases peak within 3 months of chemoradiation completion, although longer time periods have been reported.[19] Thereafter, radiographic changes might stabilise and ultimately improve. RANO guidelines have been widely used in daily practice and clinical research. Specifically, RANO criteria state that progressive disease should be diagnosed radiographically no sooner than 3 months after completion of concomitant radiotherapy and temozolomide chemotherapy, unless new enhancement outside the main radiation field occurs or unequivocal tumour progression has been pathologically confirmed. Furthermore, RANO criteria permit patients with progressive radiographic findings of unclear aetiology to continue therapy pending follow-up imaging.

Important issues regarding progressive imaging findings in patients with neuro-oncological malignancies treated with immunotherapy suggest that further adaptation of RANO criteria is warranted. First, the mechanism underlying pseudoprogression after immunotherapy is probably distinct from the mechanism associated with radiotherapy and temozolomide chemotherapy, with important differences in kinetics, frequency, and overall effect for patients. For example, although the temporal window for pseudoprogression

Lancet Oncol 2015; 16: e534–42

See Online for podcast interview with Hideho Okada

*Contributed equally

Department of Neurological Surgery, University of California, San Francisco, CA, USA (Prof H Okada MD); **Department of Neurology, University Hospital Zurich, Zurich, Switzerland** (Prof M Weller MD); **Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA** (R Huang MD); **Department of Neuro-Oncology, Istituto Neurologico Besta, Milan, Italy** (G Finocchiaro MD); **Neuro-Oncology Branch, National Institutes of Health, Bethesda, MD, USA** (M R Gilbert MD); **Department of Neurooncology** (Prof W Wick MD) **and Department of Neurosurgery, Division of Experimental Neurosurgery** (Prof C Herold-Mende PhD), **Heidelberg University Hospital, Heidelberg, Germany; Departments of Radiological Sciences, Bioengineering, Biomedical Physics, and Psychiatry** (B M Ellingson PhD), **Department of Radiology** (W B Pope MD), **and Department of Neurosurgery** (R Prins PhD), **David Geffen School of Medicine University of California, Los Angeles, CA, USA; Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan** (N Hashimoto MD); **Department of Neurological Surgery** (Prof I F Pollack MD) **and Department of Radiology** (A Panigrahy MD), **University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; Department of Medical Oncology, Azienda USL–IRCCS Institute of Neurological Science, Bologna, Italy** (A A Brandes MD, E Franceschi MD); **Center for Neuro Oncology, Dana-Farber**

Cancer Institute, Boston, MA, USA (L Nayak MD, Prof P Y Wen MD, D A Reardon MD)**; and Department of Neurosurgery, Duke University School of Medicine, Durham, NC, USA** (Prof J H Sampson MD)

Correspondence to: Prof Hideho Okada, Department of Neurological Surgery, University of California, San Francisco, CA 94158-0520, USA
hideho.okada@ucsf.edu

after radiotherapy and temozolomide generally peaks within 3 months, the timeframe for immunotherapy-associated pseudoprogression remains to be defined and might differ by the class of immunotherapy given. Second, RANO criteria do not permit treatment continuation beyond actual tumour progression because subsequent therapeutic benefit supporting this practice has not been documented for oncology treatments other than immunotherapies. Third, the appearance of a new lesion outside the main radiation field automatically defines progressive disease by RANO criteria.

Interpretation of worsened radiographic findings after immunotherapy

The interpretation of decreased size of an enhancing lesion is straightforward as such changes indicate a true anti-tumour effect because immunotherapeutics are not associated with pseudoresponse. By contrast, correct interpretation of progressive imaging findings after administration of immunotherapy is essential because early progressive radiographic changes do not always preclude subsequent therapeutic benefit.[22–32] Two main explanations exist for a possible disconnect between early worsened imaging findings and subsequent therapeutic benefit. First, effective immune responses might need time to evolve, and early imaging might reflect true progressive disease, including the development of new lesions. Nonetheless, once induced, an effective anti-tumour immune response might subsequently lead to clinical benefit. Second, because the mode of action might include an inflammatory response in areas of macroscopic and microscopic infiltrative tumour, localised inflammatory responses might mimic radiological features of tumour progression with increased enhancement and oedema.[33]

In an evaluation[22] of 487 patients with advanced melanoma treated with ipilimumab in three phase 2 studies, four patterns of radiographic response were observed. Two of these response patterns were captured by conventional WHO or RECIST criteria including radiologic response in baseline lesions with no new lesions and stable disease, which was followed by slow progressive decrease in tumour burden in some patients. Two other previously unrecognised patterns of response were not captured by conventional response assessment criteria. In some patients, an increase in size of existing lesions was followed by radiographic response or stable disease without the addition of further therapy other than ipilimumab. In other patients, new lesions were noted early on, but subsequent response or stable disease was later achieved without alternative therapeutic intervention.

Additional examples also emphasise the potential for early imaging worsening to be misleading in patients undergoing immunotherapy. First, spider plots that assess the percentage change in target lesion size from baseline over time for individual patients treated with anti-PD-1/PD-L1 therapy show enlargement of the initial tumour or even new lesions in some patients with melanoma before eventual decrease in tumour size.[26,28,31] Second, in an assessment[22] of 227 patients treated with ipilimumab, 22 (10%) patients who met WHO imaging criteria for progressive disease subsequently showed clinical benefit, including five patients who ultimately achieved partial response, and 17 patients who achieved stable disease. In a phase 2 study[34] of tremelimumab, another anti-CTLA-4 monoclonal antibody, eight patients showed a partial response of target lesions as measured by RECIST criteria concurrent with new lesions in six of the eight patients and progression of non-target lesions in two of the other patients. Of note, overall survival of these eight patients ranged from 21 to 39 months, whereas the median survival for all enrolled patients was 10·0 months. These examples underscore a potential disparity between early worsening on imaging assessment and ultimate clinical benefit including improved survival in patients treated with immunotherapy.

The frequency of ultimate clinical benefit after early progressive imaging findings in patients with neuro-oncology malignancies undergoing immunotherapy is unknown. Preliminary results of initiated clinical trials assessing immune checkpoint blocking antibodies in patients with recurrent glioblastoma (NCT02054806 and NCT02017717) and vaccines in patients with WHO grade 2 low-grade glioma (NCT01678352) show that early progressive radiographic changes (figure 1) or appearance of new enhancing lesions (figure 2) might subsequently stabilise or disappear.

New lesions

Appearance of new lesions is a criterion that defines progression of disease by RANO criteria and the Macdonald criteria. However, transient appearance of new enhancing lesions at either local or distant sites might occur in patients with neuro-oncological malignancies receiving immunotherapy (figure 2).[25,36] For cases of pseudoprogression, histopathology typically shows remarkable immune-cell infiltration, such as CD8+ T lymphocytes, but not mitotically active tumour cells.[25] In such situations, careful radiological and clinical assessments are warranted. In some cases, new enhancing lesions might represent immune responses directed against infiltrative brain tumour cells.

Confirmation of radiographic progression to define progressive disease

The immune-related response criteria were issued to aid the interpretation of imaging changes in patients with cancer undergoing immunotherapy.[22,24,37] Their intent was to raise awareness that traditional imaging criteria to define progressive disease might be less reliable and could lead to premature discontinuation of potentially beneficial therapy. A key component is the concept of confirmation of radiographic progression. Immune-related response criteria guidelines state that early

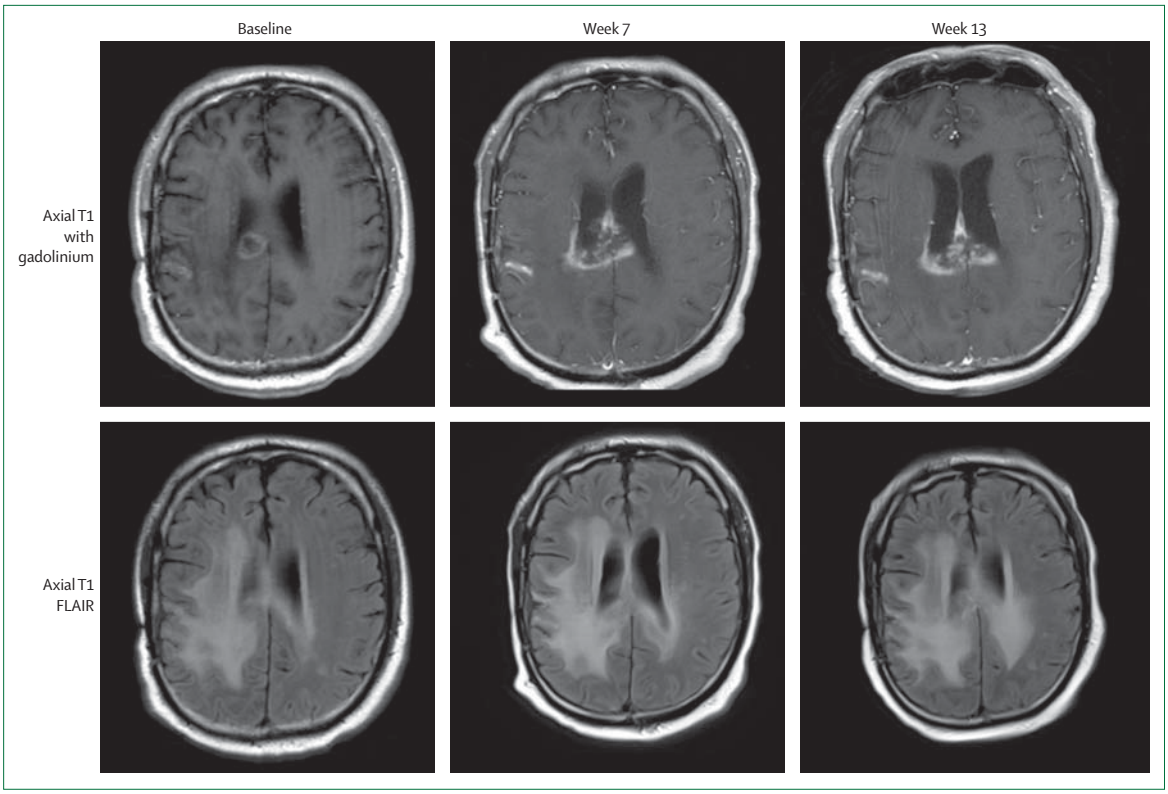

Figure 1: **Axial T1 contrast gadolinium-enhanced and FLAIR images before initiation of CTLA-4 immune checkpoint blockade 7 and 13 weeks after therapy.**[35] Although progressive findings were noted at week 7, imaging at week 13 revealed stable disease. Clinically, the patient remained stable and corticosteroid dosing remained stable at 2 mg once a day. FLAIR=fluid-attenuated inversion recovery.

increases in lesion size or new lesions do not define progressive disease unless further progressive changes are confirmed upon follow-up imaging, provided that patients do not have a clinical decline. Confirmation to define progressive disease is an important, novel aspect of immune-related response criteria, although the converse argument, the need of follow-up imaging to confirm a radiographic response, has been an accepted component of most response assessment metrics including RANO. Particularly for indications such as glioblastoma, for which few effective therapeutic interventions exist and for which durable responses are elusive, continuation of immunotherapies beyond initial progression might lessen the likelihood of prematurely discontinuing potentially effective therapy.[2,22,24]

When is confirmation of radiographic progression appropriate?

A crucial issue is identification of patients who develop early progressive imaging findings but still derive therapeutic benefit from immunotherapy from those patients who are truly resistant to therapy and unlikely to benefit clinically from immunotherapy. According to most response assessment criteria, including RANO, patients with substantial neurological decline, irrespective of imaging findings, are deemed to have progressive disease, provided that their decline is not attributable to comorbid events such as seizures or changes in medication, notably a decreased corticosteroid dosing. For such patients, radiographic confirmation of progressive disease is neither necessary nor appropriate and the date the patient's disease progressed is the date the patient developed substantial neurological decline attributable to their underlying tumour.

Future studies need to define the time window for patients without neurological decline where early progressive imaging findings do not preclude subsequent clinical benefit. Studies[2,26,28,31] show that most patients with solid tumours who benefited from immune checkpoint blockade antibodies have stable or improved radiographic findings within 6 months of starting therapy, including those who have early progressive radiographic findings. The kinetics of pseudoprogression or delayed response after various types of immunotherapy in patients with neuro-oncological malignancies needs prospective assessment. Nonetheless, anecdotal reports of patients with glioma treated with tumour vaccination therapy have described pseudoprogressive radiographic findings that typically manifest within 6 months of starting treatment.[25,36,38]

Conversely, no evidence exists that patients develop a delayed clinical benefit or radiographic response if they

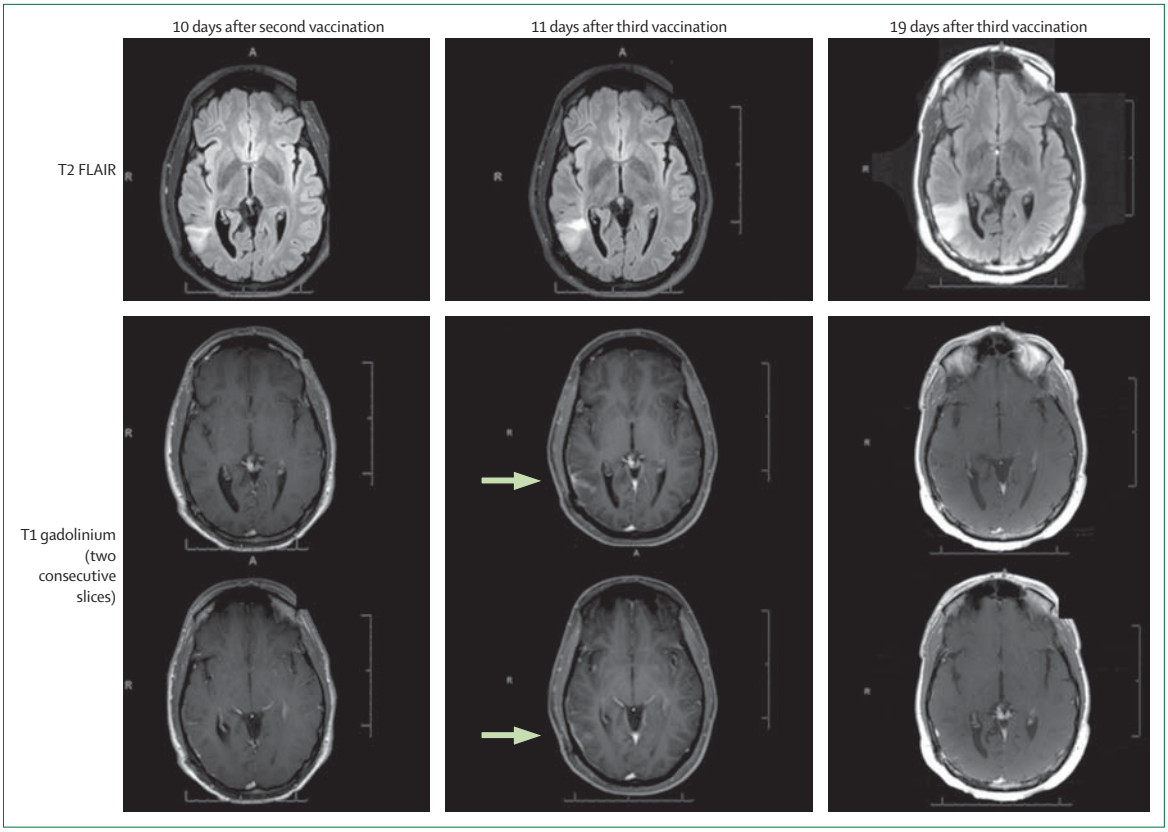

Figure 2: **Axial T2 FLAIR and T1 gadolinium-enhanced images obtained after second vaccination (left), at 11 days after third vaccination (middle), and 19 days after third vaccination (right) in a patient with recurrent WHO grade 2 oliodendroglioma (NCT01678352)**
The patient demonstrated a transient gadolinium-enhancing lesion after the third vaccination, which disappeared with no treatments within 8 days. The arrows show new enhancing lesions. FLAIR=fluid-attenuated inversion recovery.

develop progressive radiographic findings more than 6 months after starting immunotherapy. To determine whether a 6-month window is appropriate to recommend confirmation of radiographic progression, the immunotherapy Response Assessment for Neuro-Oncology (iRANO) working committee advocates that the pseudoprogression timeframe should be prospectively assessed in future immunotherapy trials.

3-month period to confirm radiographic progression

Another crucial unanswered question regarding the significance of early progressive imaging findings is how long such changes can evolve before clinicians can confidently conclude that they indicate true underlying tumour progression. Is there a period of time in which imaging findings might continue to worsen but a patient might still derive clinical benefit? Alternatively, how long should progressive imaging continue after starting immunotherapy to confidently conclude that ultimate clinical benefit is unlikely?

The immune-related response criteria guidelines recommend confirmation of progressive disease with follow-up imaging at least 4 weeks from the initial scan documenting progressive disease.[22] Yet, 4 weeks might be too early to accurately ascertain the cause of early progressive imaging changes and conclude that eventual clinical benefit is unlikely. In fact, spider plots describing changes in tumour volume over time for patients with solid tumours undergoing immune checkpoint blockade therapy show that early progressive radiographic findings typically stabilise or improve within 3 months for most patients who ultimately derive clinical benefit.[26,28,31] Similarly, a 3-month window has been defined by the RANO criteria to establish the cause of progressive imaging changes in patients with malignant glioma after radiotherapy and temozolomide chemotherapy.[14,39]

On the basis of these observations, the iRANO working committee recommends that for patients with early progressive imaging findings, including patients who develop new lesions but who do not have substantial neurological decline, confirmation of radiographic progression by follow-up imaging should be sought 3 months after initial radiographic evidence of progressive disease to decrease the likelihood of prematurely declaring progressive disease in patients with pseudoprogression or delayed response. Imaging

within the 3-month follow-up can be done as medically appropriate at the discretion of the treating clinician.

In such patients, those with confirmation of further radiographic progression based on a comparison with the scan that first showed evidence of disease progression, or who develop substantial clinical decline at any time, should be classified as having progressive disease with the date of disease progression back-dated to the first date that the patient met criteria for radiographic progression. For these patients, immunotherapy should be discontinued. In the event that follow-up imaging does not confirm further disease progression compared with the scan of the tumour that first showed initial progressive changes, but instead there is stabilisation or reduction in tumour burden, treatment should be continued or resumed in the absence of increased corticosteroid dosing. We used a treatment algorithm to summarise guidance for follow-up imaging after initial progressive changes (figure 3).

Tissue acquisition to aid response assessment

In uncertain cases in which acquisition of tumour histopathology by biopsy or resection is thought to be feasible, pathological assessment might be considered to clarify the cause of progressive imaging findings. If pathology confirms a predominance of recurrent tumour, the cause should be considered to be true progression. For cases where there is no evidence of a viable tumour, or where a prominence of gliosis or inflammation with restricted viable tumour is reported, the cause should be deemed consistent with treatment effect, and such patients should be classified as stable and allowed to continue therapy.

Although thought to be the gold standard, interpretation of tumour tissue might be challenging. Biopsies typically acquire very small tissue aliquots and thus might be subject to sampling artifact. Additionally, many specimens will show mixed findings, indicating the presence of viable tumour and treatment effect (inflammation, necrosis, etc) and guidance on appropriate interpretation of such specimens is not yet available. Neuropathologists and neuro-oncologists should prospectively prioritise the careful assessment of histopathological samples obtained from patients undergoing immunotherapy to improve their understanding of the significance of various patterns of mixed tissue findings.

Immunotherapy continuation pending confirmation of progression

Whether continued immunotherapy after initial disease progression would provide treatment efficacy or harm to patients has not yet been established and further study of this important question is warranted. A decision of whether a patient should continue immunotherapy pending confirmation of radiographic disease progression should be established based on perceived benefits and risks. Continuation of immunotherapy might be considered pending follow-up imaging as long as patients are deriving apparent clinical benefit with minimal and acceptable toxic effects. By contrast, clinicians might consider interrupting immunotherapy for patients who need a substantial increase in corticosteroids (ie, >4 mg of dexamethasone or equivalent per day) for evolving symptoms associated with cerebral oedema or who have more than mild treatment-related toxic effects such as at least grade 2 immune-related adverse events.

Although somewhat arbitrarily set and not based on definitive data, these guidelines are included to limit the likelihood of progressive immunotherapy-induced inflammatory changes leading to substantial deficits in otherwise stable or symptom-free patients. In such patients, an interruption of immunotherapy dosing might be considered pending follow-up imaging. Furthermore, one might choose to discontinue or interrupt immunotherapy at any time if this option seems to be in the best medical interest of the patient. As a general guidance, resumption of immunotherapy might

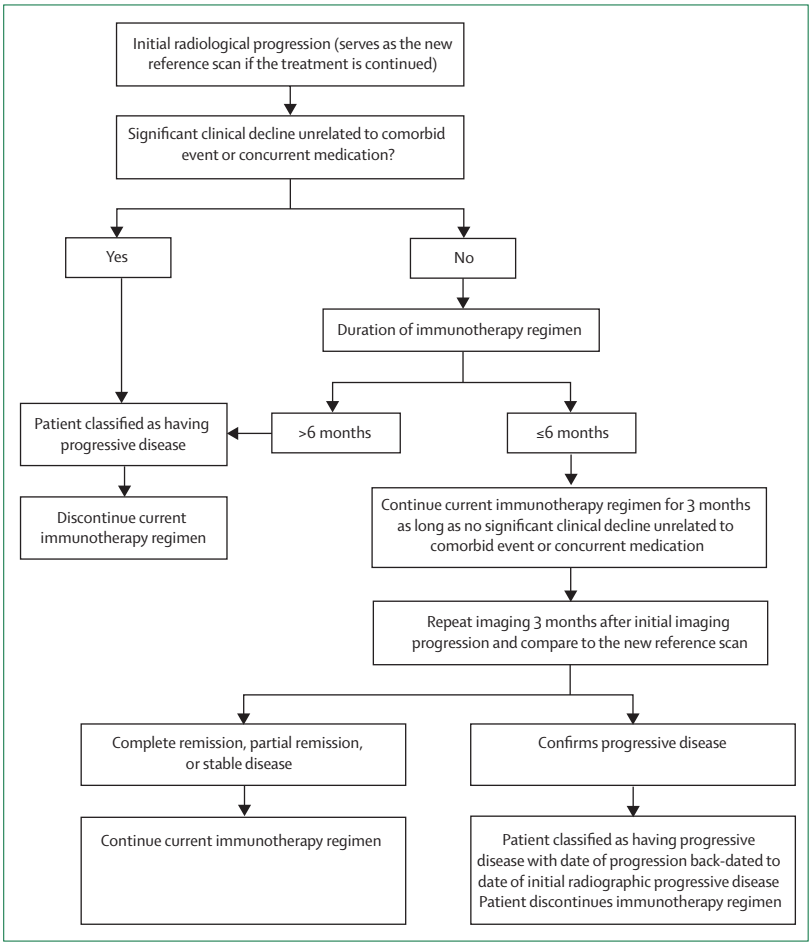

Figure 3: **iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy**
iRANO=immunotherapy Response Assessment in Neuro-Oncology.

be taken into account when systemic dexamethasone is decreased to 4 mg/day or less and the gadolinium-enhancing tumour burden is classified as stable disease, partial response, or complete response on a follow-up scan, or when relevant treatment-related toxic effects have resolved to grade 1 or less or pre-treatment baseline.

iRANO criteria

The iRANO guidelines incorporate criteria previously defined by the RANO working committee to define complete response, partial response, minor response, stable disease, progressive disease, and non-evaluable disease for patients with malignant glioma,[16] low-grade glioma,[40] and brain metastases.[18] The key component of the iRANO criteria is specific additional guidance for the determination of progressive disease in patients with neuro-oncological malignancies undergoing immunotherapy (table 1, figure 3). Specifically, the iRANO criteria advocate for the confirmation of radiographic progression in appropriate patients defined by clinical status and time from initiation of immunotherapy.

In patients who have imaging findings that meet RANO criteria for progressive disease[16–18] within 6 months of starting immunotherapy including the development of new lesions, confirmation of radiographic progression on follow-up imaging before defining the patient as non-responsive to treatment might be needed provided that the patient does not have new or substantially worse neurological deficits. Such patients might be allowed a window of 3 months before confirming disease progression with the scan that first showed initial progressive changes as the new reference scan for comparison with subsequent imaging studies. If RANO criteria for progressive disease are met on the follow-up scan 3 months later, non-responsiveness to treatment should be assumed, and the date of progressive disease should be back-dated to the initial date when it was first identified (table 1). Patients who develop substantial new or worsened neurological deficits not due to comorbid events or a change in co-administered medication at any time within the 3-month follow-up window should be designated as non-responsive to treatment and should discontinue immunotherapy. For these patients, the date of actual tumour progression should also be back-dated to the date when radiographic progressive disease was initially identified.

If radiographic findings at the 3-month follow-up meet RANO criteria for stable disease, partial response, or complete response[16–18] compared with the original scan meeting criteria for progression, and no new or worsened neurological deficits are identified, such patients should be deemed as deriving clinical benefit from therapy and allowed to continue treatment. Patients who develop worsening radiographic findings compared with the pre-treatment baseline scan more than 6 months from starting immunotherapy are expected to have a low likelihood of ultimately deriving clinical benefit and should be regarded as non-responsive to treatment with a recommendation to discontinue therapy.

Overall, we have integrated guidance from the immune-related response criteria regarding interpretation of progressive imaging findings with existing RANO criteria to form the iRANO guidelines. A comparison of the key features associated with RANO, immune-related response

	Malignant glioma[16]	Low-grade glioma[17]	Brain metastases[18]
Complete response	Disappearance of all enhancing disease for ≥4 weeks; no new lesions; stable or improved T2/FLAIR; no more than physiological steroids; clinically stable or improved	Disappearance of all enhancing and T2/FLAIR disease for ≥4 weeks; no new lesions; no more than physiological steroids; clinically stable or improved	Disappearance of all enhancing target and non-target lesions for ≥4 weeks; no new lesions; no steroids; clinically stable or improved
Partial response	≥50% decrease in the sum of biperpendicular diameters of enhancing disease for ≥4 weeks; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	≥50% decrease in the sum of biperpendicular diameter of T2/FLAIR disease for ≥4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved	≥30% decrease in sum of longest diameters of target lesions for ≥4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved
Minor response	NA	25–49% decrease in the sum of biperpendicular diameters of T2/FLAIR disease for ≥4 weeks; no new lesions; clinically stable or improved	NA
Stable disease	Does not qualify for complete response, partial response, or progressive disease; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	Does not qualify for complete response, partial response, or progressive disease; no new lesions; stable or improved T2/FLAIR; stable or decreased steroid dose; clinically stable or improved	Does not qualify for complete response, partial response, or progressive disease
Progressive disease	≥25% decrease in the sum of biperpendicular diameters of enhancing disease; or new lesions; or substantial worsened T2/FLAIR; or substantial clinical decline	≥25% decrease in the sum of biperpendicular diameters of T2/FLAIR disease; or new lesions; or substantial clinical decline	≥20% decrease in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline

The iRANO criteria integrate into the existing RANO criteria for malignant glioma, low-grade glioma, and brain metastases by providing recommendations for the interpretation of progressive imaging changes. Specifically, iRANO recommends confirmation of disease progression on follow-up imaging 3 months after initial radiographic progression if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy. If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression. The appearance of new lesions 6 months or less from the initiatiation of immunotherapy alone does not define progressive disease. FLAIR=fluid-attenuated inversion recovery. iRANO=immunotherapy Response Assessment in Neuro-Oncology. N/A=not applicable.

Table 1: **RANO and iRANO criteria**

	RANO[16]	Immune-related response criteria[22]	iRANO (if ≤6 months after start of immunotherapy)	iRANO (if >6 months after start of immunotherapy)
Is a repeat scan needed to confirm radiographic progressive disease for patients without significant clinical decline?	No	Yes	Yes	No
Minimum time interval for confirmation of disease progression for patients without significant clinical decline	N/A	≥4 weeks	≥3 months	N/A
Is further immunotherapy treatment allowed after initial radiographic progressive disease (if clinically stable) pending disease progression confirmation?	N/A	Yes	Yes	N/A
Does a new lesion define progressive disease?	Yes	No	No	Yes

iRANO=immunotherapy Response Assessment in Neuro-Oncology. N/A=not applicable.

Table 2: **Key considerations for RANO criteria, immune-related response criteria, and iRANO criteria**

criteria, and iRANO are summarised (table 2). Although application of immunotherapies for patients with neuro-oncological malignancies is in the early stages of development and much remains to be learned, the iRANO criteria provides guidelines that can be applied to provide consistent metrics in clinical trials and daily practice. Particularly, these guidelines shall raise awareness of the possibility of potentially misleading early progressive radiographic changes after initiation of immunotherapy, and provide guidance for responding to these changes to decrease the likelihood of inappropriate premature therapy discontinuation. We expect the iRANO guidelines will be amended successively to improve their usefulness as further experience and systematic data from continuing immunotherapy trials in neuro-oncology accumulate.

Corticosteroids

Patients with brain tumours frequently develop peritumoral oedema needing treatment with corticosteroids. Dexamethasone is the most commonly used corticosteroid.[41,42] In addition to the systemic side-effects, dexamethasone can have profound effects on contrast enhancement for neuroimaging studies and on the immune system, especially T cells.[43] In preclinical studies, administration of dexamethasone to rats with intracranial C6 glioblastomas dose-dependently decreased intratumoral infiltration by lymphocytes and microglial cells,[44] and limited cytokine-mediated anti-tumour effects and survival of rats bearing 9L gliomas.[45]

Several clinical studies have shown that dexamethasone can inhibit maturation of dendritic cells and subsequently their potential for antigen presentation.[46,47] In patients with cancer receiving immunotherapy, dexamethasone can also impair natural-killer-cell activity.[48] In patients with glioblastoma, treatment with dexamethasone favours the emergence of a population of CD14+ HLA-DR$^{low/-}$ monocytes that inhibit T-cell proliferation.[49]

Most of the data for the effect of corticosteroids on immune system activity derive from the assessment of high dosing schedules. By contrast, minimal data exist for the effects of differential doses,[50,51] whereas the long-term effects of low-to-moderate dexamethasone doses on immune-cell function remain unclear. Nonetheless, in view of its potential negative effects on dendritic cell, T-cell, and natural-killer-cell function, dexamethasone doses and duration of therapy should be limited to the minimum amount needed to control neurologic symptoms.

As a general guideline, patients enrolling in immunotherapy trials should have as little dexamethasone as possible before starting treatment. If pseudoprogression occurs during the course of treatment, higher doses of corticosteroids might be necessary to control symptoms. Although this might potentially reduce immunotherapy efficacy, available data are inconclusive. In a trial assessing the efficacy of ipilimumab for patients with melanoma who have brain metastases, patients who needed corticosteroids during study therapy had a worse outcome.[52] Although this could be due to the negative effect of the corticosteroids on immune function, the group needing corticosteroids could have had larger tumours and worse prognostic factors than the group who did not need corticosteroids.

Of note, patients who need increased corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment, cannot be classified as having a complete response, partial response, or stable disease and should be classified as non-evaluable at that timepoint. Conversely, patients who decrease corticosteroid use within 2 weeks of MRI assessment relative to the dose taken at the time of the previous assessment cannot be classified as having progressive disease and should be classified as non-evaluable. Recent advances in imaging techniques and measurement of clinical benefit endpoints including neurological and immunological functions are shown in the appendix.

Conclusion

We propose updated response assessment criteria for the assessment of patients with neuro-oncological malignancies undergoing immunotherapy. These recommendations integrate the framework of response assessment established by the RANO working group for malignant glioma,[16] low-grade glioma,[40] and brain metastases[18] with guidance for confirmation of disease progression as originally advocated by the immune-related response criteria to guide clinical decision making. The iRANO guidelines specifically address interpretation

Search strategy and selection criteria

We did a systematic search of articles in PubMed using combinations of the keywords: "glioma", "glioblastoma", "immunotherapy", "imaging", "corticosteroid", and "response criteria". Articles were also identified through searches of the authors' own files. We included only articles published in English between Jan 1, 1980, and March 31, 2015. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

of initial progressive imaging findings in the context of patients with neuro-oncological malignancies with a goal of decreasing the likelihood of premature discontinuation of potentially beneficial therapies while ensuring maximum patient safety. The iRANO guidelines will inevitably need future amendment, including possible incorporation of advanced imaging techniques, once sufficient experience and expertise are acquired for each of the major classes of immune-based therapies in patients with neuro-oncological malignancies. Prospective assessment of the iRANO criteria in clinical trials for patients with brain tumours undergoing immunotherapy trials will be needed to confirm their ultimate clinical usefulness.

Contributors

All authors contributed to the conception and design of the guidelines, writing, review, and revision of this Review.

Declaration of interests

HO received royalties for licensing of his inventions from Stemline Therapeutics and Intrexon. MW received personal fees from Celldex, Immunocelular, Northwest Biotherapeutics and Magforce, grants from Acceleron, Actelion, Alpinia Institute, Bayer and Piqur, grants and personal fees from Isarna, MSD, Merck (EMD), Roche, and Novocure. MRG received personal fees from Merck, Genentech, AbbVie, Wellcome Trust, Cell Medica, and EMD Serono. MRG is also an NIH employee. WW received personal fees from Celldex and Prime Oncology, grants from MSD, Boehringer Ingelheim and Apogenix, and grants and personal fees from Roche. BME received grants from Hoffman-La Roche/Genentech and Siemens Healthcare. AAB received non-financial support from Merck Serono and Pfizer. EF received non-financial support from Hoffman-La Roche. LN received advisory board fees from Amgen. WBP received personal fees from Celldex and Tocagen. RP received grants from Northwest Biotherapeutics. PYW received speaker's bureau fees from Merck, advisory board fees from AbbVie, Cavion, Celldex, Cubist, Genentech/Roche, Midatech, Momenta, Novartis, Novocure, SigmaTau, and Vascular Biogenics. DAR received speaker's bureau fees from Roche/Genentech and Merck, advisory board fees from Novartis and Stemline Therapeutics, research grants from Celldex Therapeutics and Incyte. The other authors declare no competing interests. HO, BME, IFP, AP, WBP, RP, JHS, PYW, and DAR are funded by NIH.

Acknowledgments

We thank the following iRANO working group members for their critical review on the manuscript: Pierre-Yves Dietrich, Gavin Dunn, Gene Hwang, Michael Lim, Pedro Lowenstein, James M Markert, Christopher Moertel, Solmaz Sahebjam, and Dewen Yang. This work was supported by funding from National Institutes of Health and National Cancer Institute (R21CA117152) to HO.

References

1 Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; **363:** 411–22.
2 Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363:** 711–23.
3 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372:** 320–30.
4 Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 2014; **384:** 1109–17.
5 Sundar R, Cho BC, Brahmer JR, Soo RA. Nivolumab in NSCLC: latest evidence and clinical potential. *Ther Adv Med Oncol* 2015; **7:** 85–96.
6 Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 2014; **371:** 1507–17.
7 Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 2013; **368:** 1509–18.
8 Reardon DA, Freeman G, Wu C, et al. Immunotherapy advances for glioblastoma. *Neuro Oncol* 2014; **16:** 1441–58.
9 Wainwright DA, Nigam P, Thaci B, Dey M, Lesniak MS. Recent developments on immunotherapy for brain cancer. *Expert Opin Emerg Drugs* 2012; **17:** 181–202.
10 Jackson CM, Lim M, Drake CG. Immunotherapy for brain cancer: recent progress and future promise. *Clin Cancer Res* 2014; **20:** 3651–59.
11 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47:** 207–14.
12 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92:** 205–16.
13 Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990; **8:** 1277–80.
14 Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* 2008; **9:** 453–61.
15 Chinot OL, Macdonald DR, Abrey LE, Zahlmann G, Kerloeguen Y, Cloughesy TF. Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of antiangiogenic therapy. *Curr Neurol Neurosci Rep* 2013; **13:** 347.
16 Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; **28:** 1963–72.
17 van den Bent M, Wefel J, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol* 2011; **12:** 583–93.
18 Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol* 2015; **16:** e270–e78.
19 Radbruch A, Fladt J, Kickingereder P, et al. Pseudoprogression in patients with glioblastoma: clinical relevance despite low incidence. *Neuro Oncol* 2014; **17:** 151–59.
20 de Wit MC, de Bruin HG, Eijkenboom W, Sillevis Smitt PA, van den Bent MJ. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. *Neurology* 2004; **63:** 535–37.
21 Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol* 2008; **26:** 2192–97.
22 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **153:** 7412–20.
23 Hoos A. Evolution of end points for cancer immunotherapy trials. *Ann Oncol* 2012; **23** (suppl 8)**:** viii47–52.
24 Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst* 2010; **102:** 1388–97.

25 Okada H, Kalinski P, Ueda R, et al. Induction of CD8+ T-cell responses against novel glioma-associated antigen peptides and clinical activity by vaccinations with α-type 1 polarized dendritic cells and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in patients with recurrent malignant glioma. *J Clin Oncol* 2011; **29:** 330–36.

26 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366:** 2443–54.

27 Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol* 2014; **32:** 1020–30.

28 Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013; **369:** 134–44.

29 Okada H, Pollack IF. Do we need novel radiologic response criteria for brain tumor immunotherapy? *Expert Rev Neurother* 2011; **11:** 619–22.

30 Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* 2013; **369:** 122–33.

31 Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366:** 2455–65.

32 Hodi FS, Lawrence D, Lezcano C, et al. Bevacizumab plus Ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res* 2014; **2:** 632–42.

33 Okada H, Kohanbash G, Zhu X, et al. Immunotherapeutic approaches for glioma. *Crit Rev Immunol* 2009; **29:** 1–42.

34 Kirkwood JM, Lorigan P, Hersey P, et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. *Clin Cancer Res* 2010; **16:** 1042–48.

35 Huang RY, Neagu MR, Reardon DA, Wen PY. Pitfalls in the neuroimaging of glioblastoma in the era of antiangiogenic and immuno/targeted therapy—detecting illusive disease, defining response. *Front Neurol* 2015; **6:** 33.

36 Sampson JH, Heimberger AB, Archer GE, et al. Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *J Clin Oncol* 2010; **28:** 4722–29.

37 Hoos A, Parmiani G, Hege K, et al. A clinical development paradigm for cancer vaccines and related biologics. *J Immunother* 2007; **30:** 1–15.

38 Pollack IF, Jakacki RI, Butterfield LH, et al. Antigen-specific immune responses and clinical outcome after vaccination with glioma-associated antigen peptides and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in children with newly diagnosed malignant brainstem and nonbrainstem gliomas. *J Clin Oncol* 2014; **32:** 2050–58.

39 Brandes AA, Tosoni A, Spagnolli F, et al. Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: pitfalls in neurooncology. *Neuro Oncol* 2008; **10:** 361–67.

40 van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol* 2011; **12:** 583–93.

41 Kaal EC, Vecht CJ. The management of brain edema in brain tumors. *Curr Opin Oncol* 2004; **16:** 593–600.

42 Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in brain cancer patients: benefits and pitfalls. *Expert Rev Clin Pharmacol* 2011; **4:** 233–42.

43 Ashwell JD, Vacchio MS, Galon J. Do glucocorticoids participate in thymocyte development? *Immunol Today* 2000; **21:** 644–46.

44 Badie B, Schartner JM, Paul J, Bartley BA, Vorpahl J, Preston JK. Dexamethasone-induced abolition of the inflammatory response in an experimental glioma model: a flow cytometry study. *J Neurosurg* 2000; **93:** 634–39.

45 Benedetti S, Pirola B, Poliani PL, et al. Dexamethasone inhibits the anti-tumor effect of interleukin 4 on rat experimental gliomas. *Gene Ther* 2003; **10:** 188–92.

46 Piemonti L, Monti P, Allavena P, et al. Glucocorticoids affect human dendritic cell differentiation and maturation. *J Immunol* 1999; **162:** 6473–81.

47 Matasic R, Dietz AB, Vuk-Pavlovic S. Dexamethasone inhibits dendritic cell maturation by redirecting differentiation of a subset of cells. *J Leukoc Biol* 1999; **66:** 909–14.

48 Hsu AK, Quach H, Tai T, et al. The immunostimulatory effect of lenalidomide on NK-cell function is profoundly inhibited by concurrent dexamethasone therapy. *Blood* 2011; **117:** 1605–13.

49 Gustafson MP, Lin Y, New KC, et al. Systemic immune suppression in glioblastoma: the interplay between CD14+HLA-DRlo/neg monocytes, tumor factors, and dexamethasone. *Neuro Oncol* 2010; **12:** 631–44.

50 Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993; **33:** 583–90.

51 Wolfson AH, Snodgrass SM, Schwade JG, et al. The role of steroids in the management of metastatic carcinoma to the brain. A pilot prospective trial. *Am J Clin Oncol* 1994; **17:** 234–38.

52 Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* 2012; **13:** 459–65.