Brain metastases from common solid tumors are frequently seen – they are present in up to 50% of the patients with lung cancer, breast cancer and melanoma.

The key question in determining the optimal workflow for brain metastases, in the context of solid tumor clinical trials, is whether the primary objective of the clinical trial is to determine the overall benefit of the systemic treatment on patient outcome or the CNS benefit. In PAREXEL’s experience, regulatory authorities emphasize the overall outcome which integrates the CNS component. However, in the context of the development of treatment programs, sponsors often need robust information of the specific efficacy of a novel treatment on CNS metastases. The aim of this white paper is to address the concerns enumerated by the RANO working group [The Lancet Oncology, Volume 14, Issue 10, Pages e396 - e406, September 2013] and others by providing recommendations to our biotech and pharmaceutical sponsors based on lessons learned from clinical trials regarding implementation and workflow of response determination in brain metastases specifically. Additionally, there is a forthcoming article from the RANO group that will detail many of the gaps in the aforementioned RANO article.
SOME OF THE MAJOR CHALLENGES ADDRESSED IN THIS WHITE PAPER:

**IMAGING CONSIDERATIONS**
- Inconsistent imaging may cause bias
- Sampling bias during follow-up

**READER CONSIDERATIONS**
- Reader qualification and performance
- Reading paradigms

**ELIGIBILITY CONSIDERATIONS**
- Inclusion of patients with different tumor types potentially diluting the signal of activity
- Inclusion of patients with varied lesion measurability may dilute the signal of activity

**EFFICACY CRITERIA CONSIDERATIONS**
- Criteria that have been developed for the body compartment do not capture the needs of the CNS (i.e. lesion size and measurement methodology)

**COGNIZANT OF THESE COMMON CHALLENGES, PAREXEL RECOMMENDS THE FOLLOWING**

1. **MANAGING INCONSISTENT IMAGING**
2. **RECOMMENDATION TO AVOID SAMPLING BIAS AT FOLLOW-UP**
3. **MANAGING READER PERFORMANCE**
4. **RECOMMENDED READER PARADIGM FOR EFFICACY**
5. **ELIGIBILITY RECOMMENDATIONS**
6. **RECOMMENDED EFFICACY CRITERIA FOR BRAIN METASTASES**
7. **RECOMMENDED EFFICACY CRITERIA FOR BODY IMAGING**
8. **ROLE OF ONCOLOGIST**
1 MANAGING INCONSISTENT IMAGING

CT scanning is less sensitive than MRI for detection of brain metastases, thus MRI is strongly recommended in clinical trials when response determination in brain metastases is required.

RECOMMEND MRI SCANNING BE CONSISTENT WITH RESPECT TO:

- Sequences: T1 pre- and post-contrast (SPGR) and T2/FLAIR [additional sequences may be of value: coronal reformat of axial T1 post-contrast sequence, DWI, and ADC map]
- Slice thickness with a maximum of 3mm (1.5mm preferred) T1 pre- and post-contrast
- Slice thickness from visit to visit
- Timing of scan relative to contrast injection

2 RECOMMENDATION TO AVOID SAMPLING BIAS AT FOLLOW-UP

The RANO article states: “The timing of follow-up imaging scan is equally important because small metastases are frequently asymptomatic and without rigorously scheduled imaging, the robustness of PFS as an endpoint can be doubted.”

Currently, many protocols will anticipate clinically triggered imaging of the brain, which results in reliance on unscheduled imaging for this progression indicator. ODAC has consistently warned sponsors that inconsistent timing of scans using PFS endpoints in studies of metastatic tumors of the body can be challenged from a statistical perspective. Why should PFS endpoints in studies of metastatic tumors of the brain be exempt, especially as the MR imaging is not contributing to an increase in radiation exposure?
Managing reader performance

There are strategies to enhance reader performance

- Engage the smallest number of radiologists as possible
- Neuroradiologists should read MRI studies of CNS
- Radiologists with subspecialty training in chest/abdomen read the body imaging
- Provide training to the selected readers
- Provide easy reference (laminated guidelines) to the readers

Recommended reader paradigm for efficacy

Lack of planning concerning CNS assessments in trials of systemic treatments will pose severe challenges on the collection of meaningful endpoint data specific to the CNS. Additionally, criteria that have been developed for the body do not capture the criteria needs of the CNS. PAREXEL therefore recommends:

- Readings for response in the brain and response in the body should be performed separately and the results captured in separate CRFs. An oncologist may integrate the two radiologists’ assessments with any clinical information available and provide an overall patient status in a third CRF.
  - If PFS or response of CNS metastases is the primary endpoint in a phase 3 trial, sponsors should consider double reading with adjudication of this CNS assessment. Otherwise, single read is acceptable.
  - If PFS or response at the patient level is the primary endpoint in a phase 3 trial, double reading with adjudication of the body assessment is recommended.
- If eligibility review of brain MRI is required, it is ideal to ensure reader consistency by assigning the same neuroradiologist for all follow up efficacy reads for that patient.
The RANO article states: “The prognosis of patients and their response to local or systemic treatments varies considerably by primary tumor type, and, increasingly, by emerging molecular subtypes of cancer, even within histological groups.” For this reason, it seems reasonable to select patients with a single primary tumor type.

PAREXEL has managed similar metastatic brain imaging studies. Protocols commonly require no brain metastases at screening, no active brain metastases at screening, measurable brain metastases at screening or brain metastases that are progressing at screening despite local treatment. We have found in a recent study that approximately 20% of all screened patients thought to be clinically free of brain lesions actually had brain metastases verified by brain MRI.

Preparation is needed to minimize errors of enrollment regarding brain metastases, which includes training study coordinators on which type of protocol specific imaging exams are required and whether the scans will need to be sent for BICR (Blinded Independent Central Read). It is often challenging to collect and interpret imaging acquired prior to enrollment into a particular clinical trial. However, if determination of prior progression is an eligibility criterion, MRIs done prior to screening, such as images from radiation therapy planning or prior diagnostic MRIs, must be collected and reviewed. Clinical information, such as prior local treatment information, may also be required for eligibility. If so, a study specific “baseline clinical” form can be used to list all prior radiotherapy or local intervention details.

For example, if eligibility requires a measurable lesion and prior local treatments are allowed, PAREXEL recommends only lesions with a minimal longest diameter of 5 mm and meeting any of the following criteria to be considered measurable:

- New brain metastasis
- Brain metastases without any prior local treatment
- If local treatment for brain metastases occurred:
  - Either an existing treated lesion must have progressed (20% increase in longest diameter)
  - Or at least one measurable brain lesion must have remained free of local treatment

<table>
<thead>
<tr>
<th>Total number of patients screened</th>
<th>Number of patients n/N (%)</th>
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<tr>
<td>N=605</td>
<td></td>
</tr>
<tr>
<td>Screen failures n=211</td>
<td>120/211 [56.9]</td>
</tr>
<tr>
<td>In screening n=16</td>
<td>120/605 [19.8]</td>
</tr>
</tbody>
</table>

Figure 1. “Incidence Rate of Asymptomatic CNS Lesions in Patients With HER2+ Metastatic Breast Cancer” [San Antonio Breast Cancer Symposium–December 6-10, 2011.]
BASELINE SELECTION OF LESIONS

Target lesion selection and measurement
- Size: ≥ 5mm in long axis
- Avoid selecting necrotic or cystic lesions as target lesions if other solid lesions are present
- Measure on axial plane, preferably post-contrast T1
- Slice selection: the slice with the longest in-plane diameter should be chosen at baseline for each target lesion’s measurement
- Maximum of 5 lesions in the brain
- Calculate the Sum of Diameters (SOD) which is defined as the sum of the longest axes of all target brain lesions

Non-target lesion selection
- Include all measurable lesions not chosen as target lesions
- Lesions < 5 mm in long axis
- Multiple lesions in the brain may be grouped together and assessed collectively
- Skull and scalp lesions will be assessed by the body radiologist, not the neuroradiologist
- There is no limit on number of non-target lesions

FOLLOW-UP LESION ASSESSMENT

Target lesion assessment
- Measure all target lesions
- Continue to measure lesions even if they are < 5mm. If a lesion is visible but is too small to measure, a default value of 3 mm should be used
- Calculate the SOD
- Calculate the % increase from the nadir SOD (smallest SOD of any timepoint including baseline)
- Calculate the % decrease from the baseline SOD
- If a lesion separates to form discrete lesions on a subsequent imaging timepoint, the longest diameter of each lesion will be calculated and reported separately

Figure 2. Multiple cerebellar metastases showing two longest diameter measurements in the left cerebellum
• In the event that initially separate target lesions merge (without a plane of separation), the longest diameter of the resulting lesion will be calculated and recorded for one of the original target lesions. Zero mm measurements will be entered for the other target lesion(s) and pertinent comments will be recorded.

Determine the target lesion overall response according to the following criteria:
• CR (complete response): Absence of all lesions and the entire brain is evaluable. CR is also achieved when all target lesion(s) do not show any Gad enhancement and are completely necrotic
• PR (partial response): ≥ 30% decrease in the SOD from baseline
• SD (stable disease): Neither growth sufficient to qualify for PD nor response sufficient to qualify for PR
• PD (progressive disease): ≥ 20% increase in the SOD from nadir and at least a 5mm absolute increase in SOD from nadir, with or without worsening of neurological symptoms
• NE (not evaluable): Incomplete imaging or change in modality preventing precise measurement

Non-target lesion assessment (individual non-target lesion or group)
• CR: All lesions absent and the entire brain is evaluable. CR is also achieved when all non-target lesion(s) do not show any Gad enhancement but are completely necrotic
• Non-CR/Non-PD: Persistence of lesion(s)

PD: Growth which is sufficient to determine unequivocal progression of non-target lesion(s) with or without worsening of neurological symptoms
• NE: Incomplete imaging or other causes preventing assessment of lesion(s)

Determine the non-target overall response according to the following criteria:
• CR: All lesions are absent and all lesions are evaluable. CR is also achieved when all non-target lesion(s) do not show any Gad enhancement and are completely necrotic
• Non-CR/Non-PD: Meets none of criteria above (not PD, not NE, not CR)
• PD: Any individual non-target lesion (or group) response is PD
• NE: Any lesion is not evaluable and no lesions are PD

New lesions
• Equivocal
  - A new lesion which is definitely present but may not represent malignancy or a new lesion which may be present but is either too small, too ill-defined to be certain, or is a potential artifact
  - Equivocal new lesions do not trigger PD at the current timepoint. If an equivocal lesion becomes unequivocal at a later timepoint (e.g. due to growth), the time of progression is dated back to the timepoint of that lesion’s first recognition
  - Equivocal new lesions prevent an overall assessment of CR
• Unequivocal
  - A lesion which is considered new and malignant, that is not attributable to differences in scanning technique or findings, irrespective of its size
  - Unequivocal new lesions trigger PD

Special circumstances
• New significant edema with a mass effect if it corresponds to a Gad enhancing lesion or leptomeningeal disease are considered new lesion
• Lesions detected in areas not scanned and documented at baseline are considered unequivocal new lesions and will trigger PD

Reappearing lesions
• If overall response at prior timepoint is not CR:
  - Re-measure the lesion and add the value to the SOD. PD will be triggered if the SOD increases ≥ 20%, the actual SOD increase is ≥ 5 mm, and at least one other target lesion of any size is present
  - If overall response at prior timepoint is CR:
    • Re-appearance of any target lesion is considered an unequivocal new lesion and will trigger PD
    • Any unequivocal reappearing non-target lesion will trigger PD
    • Hemorrhage is not a non-target and is not a new lesion
If the effects of treatment on CNS metastases from solid tumors are of interest, PAREXEL recommends that the assessment of body imaging is reported on a separate CRF from the CNS imaging.

The read should be performed by a different radiologist than the neuroradiologist reading the CNS imaging, preferably a reader with advanced training in body imaging and experience with RECIST 1.1 criteria. Imaging of the head and neck, outside the brain will be included in the body imaging review.

After the CNS and body images have been read, an oncologist may:

- Evaluate the CRF completed by the neuroradiologist during the CNS review
- Evaluate the CRF completed by the body radiologist during the body imaging review
- Review clinical data
- Evaluate treatment related signs and symptoms
- Evaluate tumor related signs and symptoms
- Complete a separate CRF
CONCLUSION

As with any other criterion involving tumor measurements, the key to accurate, reproducible assessment of response to treatment in both clinical practice and clinical trials is the involvement of radiologists experienced in oncological imaging. The assessment of response not only requires precise tumor size measurements, but also requires an in-depth understanding of the complications of cancer therapies and a detailed knowledge of the disease-specific tumor patterns.

PAREXEL’s aim is to reduce variability for our sponsors by selecting the best qualified radiologist subspecialists and to establish up front, clear image acquisition and analysis rules.

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