New guidelines on clinical trial design for patients with brain metastases

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D. Ross Camidge, M.D., Ph.D., and colleagues report new guidelines for clinical trial design in patients with brain metastases. Credit: University of Colorado Cancer Center

Clinical trials of new anti-cancer therapies have often excluded patients whose disease has spread to the brain or central nervous system (CNS) or, if such patients were allowed on trial, trials have often failed to

clearly capture information on the drug's effect in the brain. Today new guidelines from an international, multidisciplinary group published in the journal *Lancet Oncology* describe how to most appropriately address cancer patients with CNS involvement within clinical trials of anti-cancer drugs.

"Two major situations needed to be optimized. Firstly, as we've actually started to see some new anti-cancer drugs working well inside the brain, we needed to find a way to appropriately include these patients in clinical trials so that the trials could accurately capture that benefit. And secondly, for drugs that would be unlikely to work in the brain, we needed to limit risks to patients and to the drug development process," says D. Ross Camidge, MD, Ph.D., Joyce Zeff Chair in Lung Cancer Research at the University of Colorado Cancer Center, director of Thoracic Oncology at the CU School of Medicine and the lead author of the trial design guidelines.

The expert working group which developed these guidelines, called the Response Assessment in Neuro-Oncology—Brain Metastases (RANO-BM) group, also includes researchers from Dana-Farber Cancer Institute, City of Hope National Medical Center, Cleveland Clinic, University of Heidelberg in Germany, University of California at San Francisco, Queen's University in Canada, University of Groningen and Erasmus University Medical Center in the Netherlands, University of Turin in Italy, Massachusetts General Hospital, University of Virginia, M.D. Anderson Cancer Center, and Columbia University Medical Center.

"Historically, patients with brain metastases were excluded from the majority of systemic therapy trials for a number of reasons, including the misperception that they are poor clinical trial candidates. However, many studies show that select patients with brain metastases can safely enroll on clinical trials, without harm to the patient or to the drug

development process," says Eudocia Lee, MD, MPH, assistant professor of Neurology at the Center for Neuro-Oncology at the Dana-Farber Cancer Institute and co-lead author of the guidelines.

The guidelines adopt a pragmatic approach, suggesting one of three specific strategies based on initial understanding of a drug's possible activity in the brain. First, when a new drug is considered very unlikely to have activity in the brain, patients with stable CNS disease should be permitted, while those with active CNS disease should be excluded from trials of systemic therapy. Second, if there is some initial evidence that a drug may have activity in the brain, the guidelines propose including patients with both stable and active CNS disease in a way that will capture data defining a drug's activity in the brain separate from its activity in the rest of the body. Third, when it's unclear whether a drug may have activity in the brain (as is often the case at the start of any new drug development process), the guidelines suggest including a dedicated cohort of patients with brain metastases very early in drug development to generate the data that would allow trial designers to adopt one of the other two trial designs.

The new guidelines reflect the contributors' firsthand experiences developing new targeted therapies across cancer subtypes.

"For some subtypes of breast cancer, including HER2-positive or triple-negative, the incidence of brain metastases in patients who have recurrent/metastatic disease approaches 50 percent. Making progress against these subtypes of breast cancer very much depends on developing new and better treatments for brain metastases. Our hope is that by providing investigators with a roadmap for clinical trial design, we can encourage more studies focused on this challenging clinical problem. These new guidelines aim to fundamentally change drug development for advanced cancers," says Nancy U. Lin, MD, clinical director of the Breast Oncology Center at the Susan F. Smith Center for

Women's Cancers at Dana Farber Cancer Institute.

"Brain metastases are also very common in lung cancer and it would be very frustrating to have a patient with controlled brain disease excluded from a trial that could benefit them," says Camidge, who has been intimately involved with the development of targeted therapies against non-small cell lung cancer, including crizotinib, alectinib and brigatinib. "Similarly, we have also started to see anecdotal evidence of new targeted therapies working against metastases in the brain, but current clinical trial design leaves holes in the data. For example, many trials don't standardize capturing information on the use of prior radiotherapy in the brain and so in such cases it has been very hard to tell whether benefit in a patient's CNS disease was due to radiotherapy or to the drug. When trying to choose between treatments, it was clear that we needed to get serious about demanding better data quality with respect to the brain."

The new guidelines may be especially important for clinical trials addressing patients with cancer types that commonly spread to the brain, including non-small cell lung cancer, small cell lung cancer, HER2+ and triple-negative breast cancer, and melanoma, all of which become especially dangerous once reaching the central nervous system. In these conditions, the guidelines write that, "Exclusion of [brain metastasis] patients could remove half to two-thirds of the stage IV population."

"We all hope that these guidelines will represent a turning point in cancer drug development," Camidge says. "Over the next few years, changes in clinical trial design centered around generating and acting on early signals of a drug's CNS activity or lack thereof should radically decrease risk and increase the therapeutic potential of new drugs across many different cancers."