Letter to the Editor

How do the QUARTZ trial results inform future research for patients with brain metastases from non-small cell lung cancer?

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We read with interest the editorial by Tsao (1), and thank the author for this well considered response to our recent paper describing the results of the QUARTZ trial of whole brain radiotherapy for patients with inoperable brain metastases from non-small cell lung cancer (2). We continue to be encouraged by the amount of discussion taking place surrounding treatment options for these patients.

Tsao rightly highlights that it was very challenging to recruit patients into QUARTZ. Diagnoses such as inoperable brain metastases are clearly very distressing and present a difficult setting in which to conduct a clinical trial. We would like to express our sincere thanks and admiration for the patients and clinicians who persevered with the trial and made it a success. We largely agree with the author that the lack of clinical equipoise in individual cases was a major reason for the slower than expected recruitment rate. We collected screening logs during the trial, and they highlighted that the most common reason for not entering the trial was that the clinician and/or the patient wanted to either receive or avoid whole brain radiotherapy. Whilst we were unable to record any characteristics of these patients it does point to a lack of clinical equipoise, and it would be reasonable to think that patients with better prognoses were being selected for WBRT, and those with poorer prognoses were avoiding WBRT.

One of the unusual steps undertaken in QUARTZ was to release interim trial data to investigators (3,4). We believed that the lack of existing data was one of the main reasons for the lack of clinical equipoise, and having access to some data might make clinicians and patients more comfortable with the trial randomisation. It was interesting to note that after the presentation of these data to investigators, the rate at which poor performance status patients (KPS <70) were randomised into the trial dropped slightly (from 2.9 patients per month to 2.2 per month), whereas the rate that good performance status patients were randomised increased significantly (from 3.2 patients per month to 5.3 per month). This perhaps suggests that having viewed the interim data and seen the small size of any potential benefit, clinicians/patients became more comfortable with the possibility of omitting WBRT.

This links to another important point raised by

Tsao, that patients often have misconceptions about the intentions and potential outcomes of treatment. This was something described in this specific patient population by Dorman *et al.* (5), who interviewed nine QUARTZ patients from a single centre, several of whom demonstrated a misunderstanding of both the practical requirements of WBRT and their likely prognosis. In order for patients and clinicians to make fully informed treatment decisions, they need access to accurate estimates of likely treatment effects, and trials such as QUARTZ are the best source of this information.

The author also notes the emergence of several targeted agents during the life of QUARTZ. This is an important point, and these agents appear to be good options for patients with the appropriate molecular make-up (6). However at present only a small percentage of patients have a driver mutation targetable with approved treatment (in the UK approximately 10% of NSCLC patients have an EGFR mutation and 5% an ALK-rearrangement). Nonetheless it seems reasonable to believe that this will increase as our knowledge increases and more targets are identified.

Two important outcomes from QUARTZ are: firstly that it is possible to conduct trials in this patient group; and secondly, that for the majority of patients, future trials of systemic agents can be conducted without also having to include WBRT. We agree with Tsao's closing statement that the future of brain metastases research and treatment is promising, with increasing options and hopefully more opportunities for well conducted clinical trials.

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Footnote

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