Metastases to the central nervous system (CNS) in patients with non-small cell lung cancer (NSCLC) often herald a poor prognosis and a significant decrement in quality of life. Despite the substantial number of NSCLC patients who develop CNS metastases, there are few trials specifically addressing outcomes in these patients (1); many NSCLC trials studying systemic treatment exclude patients with active brain metastases. Dr. Welsh and colleagues recently published an article addressing this understudied population. They enrolled 40 NSCLC patients with brain metastases who went on to receive WBRT with concurrent administration of the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), erlotinib (2). The results indicate that the combination is feasible and tolerable with an excellent median overall survival (OS) of 19.1 months and median CNS progression free survival (PFS) of 12.3 months.

Though the survival data for concurrent therapy appear impressive compared to cited historical controls (3-6 months), they need to be interpreted in the context of data that has become available since Dr. Welch’s trial began enrollment. Multiple studies have now demonstrated the substantial progression free survival benefit of EGFR-TKIs compared with conventional chemotherapy in the first-line treatment of patients whose tumors contain EGFR activating mutations (3,4). Longitudinal studies in patients tested for EGFR mutations indicate that patients with EGFR mutations may have prolonged OS after diagnosis of brain metastases whether treated with surgical resection, WBRT and/or stereotactic radiosurgery (SRS): 14.5 months for EGFR mutations, 7.6 months for EGFR wild-type and 11.7 months total in one published study (5), suggesting that patients with EGFR mutated tumors may survive longer independent of treatment strategy.

Patients in this study were enrolled regardless of tumor EGFR mutation status. Nine of seventeen patients (53%) with available EGFR mutation testing had tumors harboring an EGFR activating mutation, much higher than what is expected in a random sample of NSCLC patients. The authors hypothesize that the over-representation of EGFR activating mutations in their sample may indicate CNS tropism of EGFR mutated tumors. Though this is an intriguing hypothesis that deserves future exploration, selection bias in this trial is a more likely explanation for the high percentage of patients enrolled with EGFR activating mutations. Trial demographics include a younger age, higher percentage of women and higher percentage of never smokers than what is typically seen in metastatic NSCLC trials - all factors that predict for an increased percentage of EGFR activating mutations (6). OS and CNS PFS were numerically higher, and cumulative incidence of CNS progression numerically lower in the patients with EGFR mutations (though underpowered and not statistically significant) highlighting the preferential activity of erlotinib in EGFR mutated tumors.

There is growing evidence that erlotinib alone has CNS activity in NSCLC patients with EGFR activating mutations. As early as 2006, there were reports of patients with brain metastases from NSCLC who had complete CNS responses after receiving erlotinib alone. In 2012, two small studies reported CNS responses comparable to those reported by Welch et al. (Table 1). This raises a very
important question: can using erlotinib in EGFR-activated patients delay or obviate the need for WBRT, thereby avoiding the potential development of neurocognitive side effects from brain radiation (9)? The recently published LANDSCAPE trial attempted to answer a similar question in patients with brain metastases from Her2+ breast cancer, with promising results: a high CNS response rate (65.9%) was seen with the combination of capecitabine and lapatinib (an anti-Her2 TKI) (10).

In this trial, patients with EGFR wild-type or EGFR unknown tumors had numerically inferior outcomes compared to patients with EGFR mutated tumors; but overall survival (OS) and CNS progression free survival (PFS) in these patients was still better than the authors cited historical controls. The authors highlight previously published in vitro research that shows EGFR TKIs can radiosensitize EGFR-wild type tumors. Overexpression of tumor EGFR has been hypothesized to contribute to tumor resistance to radiotherapy and reduced local control (11,12). Interestingly, EGFR blockade has not shown benefit in primary CNS tumors with increased expression of EGFR, such as glioblastoma multiforme (13). Though this trial suggests erlotinib may be active in EGFR wild-type and unknown status patients, it is important to note that the number of EGFR mutants in this study was much higher than one would expect. Without definitive knowledge of the mutational status of the “unknown” group, the benefit of concurrent erlotinib and WBRT in these patients remains unclear.

Dr. Welsh and colleagues provide a welcome focus on NSCLC patients with CNS metastases - an understudied population of NSCLC patients. Though the trial is intriguing, it is limited by small sample size, selection bias and changes in the standard of care in the patients who derived the most benefit from the combination - patients whose tumors harbor EGFR activating mutations. Since recent papers suggest that erlotinib alone can effectively treat brain metastases, we believe the best use of concurrent erlotinib and WBRT is in patients with EGFR activated tumors who have active systemic disease needing treatment and have brain metastases that are either too symptomatic to wait for a potential CNS response from erlotinib or too numerous to be amenable to stereotactic radiosurgery. This trial shows combination erlotinib and WBRT can be feasible, safe and effective.

**Acknowledgements**

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**References**


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† Patients with asymptomatic brain metastases only; †† All patients regardless of EGFR mutation status


