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TARGETED THERAPIES

GLIOMA—IT'S ALL IN THE SITE OCCUPANCY

Activating mutations in *EGFR* occur in glioblastoma multiforme (GBM) and lung cancer; however, only patients with lung cancer have shown a clear response to EGFR inhibitors. Two studies published in *Cancer Discovery* shed light on the reasons behind these contrasting observations.

Ingo Mellinghoff and coauthors examined established GBM cell lines and freshly derived tumour sphere lines to assess *EGFR* mutations. "Our finding that EGFR activity is critical for the survival of *EGFR* mutant GBM cells suggests that inadequate EGFR inhibition, rather than redundancy in GBM signalling networks, may be the principal cause of drug resistance," explains Mellinghoff. He continues, "another important and unexpected finding was the differential sensitivity of GBM versus lung cancer *EGFR* mutants to EGFR kinase inhibitors. Inhibitors such as lapatinib or neratinib, which stabilize the kinase in the inactive conformation, were considerably more potent than erlotinib at inhibiting the extracellular *EGFR* mutants found in GBM." Interestingly, the researchers found that the opposite was true for the most common *EGFR* kinase domain mutations in lung cancer, which were inhibited more effectively by drugs such as erlotinib that stabilize the active conformation.

William Weiss, Theo Nicolaides and colleagues developed a covalent inhibitor of EGFR that was linked to a fluorophore to measure kinase occupancy of EGFR inhibitors. They showed that at equivalent doses, erlotinib achieved lower kinase-site occupancy in brain tumour-derived mutants of *EGFR* compared with lung cancer-derived *EGFR* mutants. Because the brain-tumour-derived mutants did not bind as much drug, this led to reduced efficacy at the same drug dose. Weiss describes the key findings, "we showed that brain tumour-derived mutants of EGFR released erlotinib more rapidly compared with lung cancer-derived mutants, suggesting that kinase-site occupancy could be a biomarker for efficacy of EGFR inhibitors, and that slower cycling of clinical EGFR inhibitors within the active site of lung cancer-derived mutants underlies their improved clinical response."

Lisa Hutchinson

Original articles Vivanco, I. *et al*. Differential sensitivity of glioma-versus lung cancer-specific EGFR mutations to EGFR kinase inhibitors. *Cancer Discov.* doi:10.1158/2159-8290.CD-11-0284 | Barkovich, K. J. *et al*. Kinetics of inhibitor cycling underlie therapeutic disparities between EGFR-driven lung and brain cancers. *Cancer Discov*. doi:10.1158/2159-8290.CD-11-0287