Curr Oncol, Vol. 19, pp. 8; doi: http://dx.doi.org/10.3747/co.19.955

GUEST EDITORIAL

EGFR tyrosine kinase inhibitors in lung cancer: make no assumptions

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The systemic treatment options and algorithm for stage IV non-small-cell lung cancer have changed tremendously since 2005, leading to improved survival and quality of life for this group of patients. But the changes have also led to confusion and complexity for the oncologist deciding on which treatments to use and the order of those treatments for the best benefit of their patients.

Tailored medicine became reality when it was concluded that patients whose tumours harbored a mutation in the gene for the epidermal growth factor receptor (*EGFR* M+) benefited from EGFR tyrosine kinase inhibitors (TKIs). In comparison with chemotherapy in the first-line setting, these new agents significantly improved response, progression-free survival, and quality of life. First-line TKI for *EGFR* M+ patients became the standard of care in most parts of the world [1].

The opposite finding was seen in patients with wild-type or mutation-negative *EGFR* (*EGFR* WT), in whom chemotherapy fared better. Although overall survival was not statistically different, on examination of the curves, *EGFR* WT patients treated with an EGFR TKI in the first line setting were clearly seen to be lost to life.

Clinical characteristics cannot accurately predict for *EGFR* M+. When treating patients in the first-line setting, make no assumptions about who is *EGFR* M+. Do no harm.

After the first-line setting, the situation is far less clear [2]. Randomized trials continue to show a marked benefit in *EGFR* M+ patients treated with an EGFR TKI, but a benefit (albeit not as large) is also evident in *EGFR* WT patients. In other words, a benefit with no harm done [3].

How can this be? The mutation under discussion is not just in any area, but in the area of the gene coding for the tyrosine kinase domain of the receptor. If an abnormal EGFR receptor is the driving force for the tumour, it makes sense that drugs that inhibit the exact area of abnormality may be efficacious in decreasing the signal. But how would they work if the receptor is normal—in other words, if a mutation has not occurred?

Many hypotheses have been put forward. Most likely, other signalling pathways take precedence. The case presented by Dr. Irene Karam in this issue of *Current Oncology* is of much interest. A white, heavy-smoking man with *EGFR* WT has had a dramatic and prolonged response to erlotinib in the second-line setting. This unexpected result illustrates the complexity of biomarker-tailored therapy in today's world.

Regulatory bodies such as the European Medicines Agency have restricted drugs in this class solely to patients who harbor *EGFR* M+ for all lines of therapy, and not just the first line. Ontario authorities have had similar discussions. This case proves that such a restriction is not correct. To deny a TKI to *EGFR* WT patients in the second-line, third-line, or maintenance settings when a benefit has been proved is wrong.

Make no assumptions about who may or may not benefit from an EGFR TKI after the first-line setting.

CONFLICT OF INTEREST DISCLOSURES

BM has received honoraria from Boehringer Ingelheim, Hoffmann–La Roche, Eli Lilly and Company, Sanofi–Aventis, and AstraZeneca Pharmaceuticals.

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