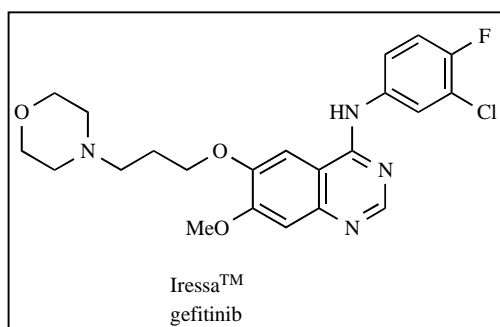


Molecule of the Month

Overcoming Resistance. Over four years ago, on May 2, 2003, the FDA approved Iressa™ (gefitinib) by AstraZeneca for the treatment of non-small cell lung cancer (NSCLC) in patients that failed to respond to two other types of chemotherapy. The potential therapeutic benefit of Iressa™, a once-daily tablet, was obvious, as the drug elicited an objective response and was well-tolerated in Phase II trials. The subsequent Phase III clinical trial, however, failed to prove that patients taking Iressa™ survived longer than those taking placebo. Due to these results, on June 17, 2005, the FDA limited the use of Iressa™ to patients who were currently benefiting or had previously benefited from the drug and patients that had formerly been enrolled in clinical trials. Importantly, although clinical trials of Iressa™ did not demonstrate a survival benefit for the overall patient population, the study showed a statistically significant increase in survival for patients of Asian origin and patients who had never smoked [1].



The epidermal growth factor receptor (EGFR) performs a critical role in cellular proliferation, differentiation and survival. Aberrant EGF-EGFR signaling, as in the case of mutations, leads to overexpression of wild-type EGFR – a hallmark of a broad range of cancers, including lung, breast and colon carcinomas [2]. Iressa™, a quinazoline derivative, is a tyrosine kinase inhibitor (TKI) that selectively targets EGFR. Despite the initial response to the drug in the majority of NSCLCs, most of the tumors eventually develop resistance to Iressa™. A secondary mutation in the EGFR gene is responsible for resistance in approximately half of these cases, but the cause of resistance in the remaining cancer cells is still being investigated. A recent study (*Br. J. Cancer* **2007**, 97, 1560-1566) determined that classical mutations in the EGFR TK domain (exons 18, 19 and 21), but not other mutations, are associated with the clinical

outcome in treated patients with NSCLC [3]. A recent study by Dr. Jeffrey A. Engelman *et al.* (*Science* **2007**, 316, 1039-1043) suggests that amplification of the MET oncogene may be another mechanism that leads to resistance, indicating combination therapy with MET kinase inhibitors as a possible solution [4].

Even if Iressa™ does not prove to be the cancer therapeutic that was hoped for, the molecule may serve as the precursor to a new effective anticancer agent. Tarceva™ (erlotinib), a joint product of Genentech, Inc. and OSI Pharmaceuticals, Inc., is a derivative of Iressa™ and another EGFR tyrosine kinase inhibitor that is currently in Phase III clinical trials [5]. Research is also being conducted to synthesize more analogues of Iressa™; Professor Jean-Pierre Henichart *et al.* synthesized 23 Iressa™ derivatives, many of which decreased proliferation and induced apoptosis in human prostate cancer cells [6]. The future of Iressa™ will be determined by further evaluation of the drug's effectiveness in subgroups, understanding of the cancer cells' resistance mechanisms, and novel therapies to overcome that resistance.

REFERENCES

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- [4] Engelman, et al. "MET Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling." *Science*, **2007**, 316, 1039-1043.
- [5] For detailed information describing Tarceva™, see www.tarceva.com
- [6] Henichart, et al. "Derivatives of Iressa, a Specific Epidermal Growth Factor Receptor Inhibitor, are Powerful Apoptosis Inducers in PC3 Prostatic Cancer Cells." *ChemMedChem*. **2007**, 2, 318-332.

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