

phase II clinical trials are often limited by their small sample sizes to detect true treatment differences between the study arms. In this study, we observed improvements in PFS and TTP...however, these findings did not translate into an improvement in OS” (26).

VIII. TIME TO PROGRESSION MAY SHOW EFFICACY, WHERE THE ENDPOINT OF OVERALL SURVIVAL FAILED TO SHOW EFFICACY, WHERE THE DURATION OF THE TRIAL WAS TOO SHORT – THE CAPPUZZO STUDY

The following study on non-small cell lung cancer (NSCLC) used the endpoints of objective response, TTP, and overall survival. Cappuzzo et al. (27) administered the same drug (gefitinib) to all study subjects. Gefitinib inhibits enzymatic activity of a particular kinase, namely, epidermal growth factor receptor (EGFR) tyrosine kinase. Cytogenetic assays were conducted on all study subjects prior to administering the drug, to determine the number of EGFR genes in tumor cells. Tumor cells were acquired via biopsies, and the number of copies of the EGFR gene in a sampling of tumor cells was determined by way of the fluorescent in situ hybridization (FISH) technique.

Twenty-five of the patients were FISH positive for EGFR. Eleven patients were FISH negative for EGFR. “FISH positive” was defined as tumor cells carrying four or more copies of the EGFR gene in 40% of the tumor cells. “FISH negative” was defined as tumor cells carrying four or more copies of the EGFR gene in less than 40% of the tumor cells.

Table 13.4 demonstrates the greater efficacy of gefitinib in patients bearing EGFR positive tumor cells (as compared to patients with EGFR negative tumor cells). This

Table 13.4 The Cappuzzo study

	Patients with EGFR positive tumors	Patients with EGFR negative tumors	Significance of difference of endpoint, comparing EGFR + and EGFR – patients
Objective response	68.0%	9.1%	P < .001
TTP	7.6 months	2.7 months	P = .02
Overall survival	Median survival not reached	7.4 months	–

²⁶ McDermott DF, Sosman JA, Gonzalez R, et al. Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. *J Clin Oncol.* 2008;26:2178–2185.

²⁷ Cappuzzo F, Ligorio C, Jänne PA, et al. Prospective study of gefitinib in epidermal growth factor receptor fluorescence in situ hybridization-positive/phospho-Akt-positive or never smoker patients with advanced non-small-cell lung cancer: the ONCOBELL trial. *J Clin Oncol.* 2007;25:2248–2255.