TABLE 14.4 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%	$P < 0.001$
TTP	7.6 months	2.7 months	$P = 0.02$
Overall survival	Median survival not reached	7.4 months	–

IX. TTP 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. (33) 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 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 EGFR gene, in 40% of the tumor cells. "FISH-negative" was defined as tumor cells carrying four or more copies of EGFR gene, in less than 40% of the tumor cells.

Table 14.4 demonstrates the greater efficacy of gefitinib in patients bearing EGFR-positive tumor cells (as compared to patients with EGFR-negative tumor cells). This greater efficacy was demonstrated with the endpoints of objective response and TTP.

The Cappuzzo study provides the take-home lesson that, to forestall data acquisition problems due to short follow-up times, it is wise to include endpoints that can be fully captured early in the clinical trial. Suitable endpoints that can be captured early in the trial include objective response (RECIST criteria) and TTP.

A schematic representation of the Kaplan–Meier plot demonstrates the striking differences in TTP that were associated with the change in EGFR gene copy number (Fig. 14.3). The authors concluded that EGFR FISH analysis is an accurate predictor for efficacy with gefitinib therapy against lung cancer. To conclude, the Cappuzzo study demonstrates that EGFR is a useful biomarker. Other biomarkers, such as HER2 and KRAS, are described in Chapter 19.

[33]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;25:2248–55.